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Archives of Internal Medicine

VOLUME 37 MAY, 1926 NUMBER 5

BLOOD PRESSURE IN WOMEN AS INFLUENCED BY THE SEXUAL ORGANS*

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AND
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SAN FRANCISCO

Several years ago when one of us (W. C. A.) analyzed the records of blood pressure in 15,000 University of California freshmen and 1,000 office patients, he was much impressed by the fact that the data from the women were so different from those of the men. Thus, when we turn to the report of that work,[1] we note, first, that the mean pressure for the women was 10 mm. less than that for the men until the late forties, when the women's pressures averaged higher than those of the men. More striking was the fact that whereas 20.7 per cent of the young men had pressures over 140 mm., only 2.7 per cent of the women were similarly affected.

In all fairness, it should be noted at this point that Diehl and Sutherland [2] have just shown that if the men students with the high readings are allowed to rest a while, or if they are examined repeatedly so that they can lose some of their nervousness, 49 per cent ultimately show lower pressures; 25 per cent will vary up and down, and 15 per cent will maintain the high level. Eleven per cent were excluded from consideration because their hypertension was thought to be of the secondary type.

At first sight, this might seem to wipe out a good deal of the difference between the pressures of men and women, but we must remember, first, that it is not good statistical practice to take just the data that fail to agree with our previous conceptions and to work with them until they do agree; if we are going to modify some of our data we should modify all of them; second, much of our own unpublished work on these boys with transient and intermittent hypertension makes us feel that their

* From the George Williams Hooper Foundation for Medical Research, and the department of medicine, University of California Medical School.

1. Alvarez, W. C.: Blood Pressure in University Freshmen and Office Patients, Arch. Int. Med. **26**:381 (Sept.) 1920; Blood Pressures in Fifteen Thousand University Freshmen, ibid. **32**:17 (July 15) 1923.

2. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men, Arch. Int. Med. **36**:151 (Aug 15) 1925.

peculiarity does mean something for their futures, and that it cannot be lightly reasoned away, and, third, even if we do discard these cases, there still remains a big difference between the incidence of hypertension in men and in women. Diehl and Sutherland found 5.6 per cent of their men students with permanent or intermittent hypertension and 1.2 per cent more with "secondary hypertension"—all over 140. This gives 6.8 per cent, which compares well with Alvarez' figure of 7.6 ± 0.2 per cent for men with pressures of 150 mm. and over—men that were almost certainly abnormal. Even if we follow Diehl and Sutherland and exclude 51 per cent of Alvarez' group of men with pressures over 140 mm., we still have 10.2 per cent to compare with the 2.7 ± 0.1 per cent among the women.

This difference between men and women can be brought out even more clearly perhaps by pointing to the fact that at the University of California there were 3.6 times as many men as women with pressures over 130, 7.5 as many with pressures over 140, 14 times as many with pressures over 150, and 30 times as many with pressures over 160 mm.

As we might have expected, this big difference between the pressures of men and women appears about the time of puberty.[3] Before that the pressures in the two sexes are about the same.[4] It is interesting also that in both the young men and the young women the pressures are highest about 17. After that they drop a little until about the age of 28 in the men, and 24 in the women. The rise that then takes place in the mean pressure is more rapid in the women than in the men, so that after 45 or 50 the women average higher than the men.

Another sexual difference comes out clearly when we compare the distribution curves based on the data from men and women. Then we see that the curves for the women are high and narrow while those for the men are low and wide. This difference appears about the age of 17. In the language of the statistician, the standard deviation and the coefficient of variation are lower for the women up to the age of 35. After that, these indexes are higher for the women than for the men.

HEREDITY AND HYPERTENSION

Now, something that appears so strikingly in college freshmen of 17 and 18 can hardly be ascribed to the wear and tear incident to old age or to the strenuous life, and something that varies so markedly in the two sexes is not likely to be due to such things as focal infections or

3. Burlage, S. R.: The Blood Pressures and Heart Rate in Girls During Adolescence, Am. J. Physiol. **64**:252 (April) 1923.

4. Judson, C. F., and Nicholson, P.: Blood Pressure in Normal Children, Am. J. Dis. Child. **8**:257 (Sept.) 1914. Faber, H. K., and James, C. A.: The Range and Distribution of Blood Pressures in Normal Children, Am. J. Dis. Child. **22**:7 (July) 1921.

intestinal autointoxication, which we would expect to find pretty evenly distributed between the two groups. If constipation has anything to do with it, we should expect to find somewhat more hypertension in the girls than in the boys.

It would seem more probable, then, that we must be dealing with some bodily peculiarity which is distinctly modified by sex, especially at the crises of puberty and the menopause. But where does the peculiarity come from? Almost certainly from our ancestors. For years one of us (W.C.A.) has been impressed by the high incidence of hypertension which he has observed in the relatives of those complaining of this disease, and a search through the literature shows that several writers have commented on the same thing. Family records such as that published by Rosenbloom [5] are striking, but the statistical studies of O'Hare, Walker and Vickers,[6] and of Weitz [7] are still more convincing. O'Hare and his associates studied 300 persons with hypertension and 436 without hypertension or other cardiovascular-renal disease. In the first group there was a history in one or more relatives of apoplexy, heart disease, nephritis, arteriosclerosis or diabetes in 68 per cent, while in the second or control group such a history could be obtained in only 37.6 per cent. Weitz found that half of the sibs of some eighty-two patients with hypertension had hypertension or had already died of it. Three fourths of their parents had died of strokes, heart disease or other conditions suggesting the presence of the hypertensive diathesis. In his control group of 267 subjects—unfortunately not so well studied—he found 30 per cent of parents with suggestive histories. Although this work leaves much to be desired from the standpoint of the geneticist and the biometrician, it is suggestive and points the way to some more extensive and more careful work by men who have had special training in this field.

THE SEXUAL FACTOR

If, then, we follow the lead of this evidence and assume that the main factor in producing hypertension is a hereditary predisposition, we must next explain the fact that the men develop it early and the women develop it late. If the women inherit the tendency equally with the men—and we have no reason to assume the presence of any sex linkage—what holds it latent in the earlier years? Certainly it would seem to be the internal secretions that have so much to do with sexual

5. Rosenbloom, J.: Familial Hypertension, with Report of a Case, J. Lab. & Clin. Med. **8**:681 (July) 1923.

6. O'Hare, J. P.; Walker, W. G., and Vickers, M. C.: Heredity and Hypertension, J. A. M. A. **83**:27 (July 5) 1924.

7. Weitz, W.: Zur Aetiologie der genuinen oder vasculären Hypertension, Ztschr. f. klin. Med. **96**:151 (Jan.) 1923.

development. As one of us [1] has pointed out, there are many things about the plumage changes that hens show after ovariectomy that are suggestive in this connection. As is well known, these hens come to look like cocks, and it may be that in women, hypertension emerges at the menopause much as hair emerges on the face—and for the same reason.

This theory would receive great support if it could be shown that a considerable proportion of young women who are born with poor ovaries, or who early in life lose a large part of the functioning tissue through disease or by operation, promptly develop hypertension. Naturally, we would not expect all such women to develop it because many of them would not be carrying the tendency. They would belong to that group of men and women who go on into their seventies with pressures under 130 mm. of mercury.

MATERIAL USED

The present study is based on the analysis of some 1,230 records taken from the office files of one of us (W. C. A.). The great advantage of these records is that they were made almost entirely by one man, who, for a good part of the time, was interested in the solution of the problem before us. The patients for the most part came complaining of gastro-intestinal troubles or, at least, what they thought were gastro-interstinal troubles, so that they have not been selected for either hypertension or ovarian disease. In all but a few cases, a pelvic examination was made, and in most of the cases in which abnormalities were found in that region, the findings were checked by an expert gynecologist. Unfortunately, in spite of this carefulness, there were a good many of the records which were not complete on all points and which could be used only for certain phases of the inquiry.

The women on whose findings this study is based were almost entirely from the middle and upper classes. All were white. The blood pressures were taken with a good mercury instrument, and the auscultatory readings were used. The diastolic pressure was taken at the end of the third phase. The patients were all reclining. When borderline pressures were found, several readings were taken during the course of the examination—usually spread over several days—and either the mean or the modal pressure was taken for the purposes of this study.

The histories were abstracted on cards on which note was made of the name of the patient, her civil status, age, number of children, menstrual history, history of pelvic disease and operations, pelvic findings, weight and build, condition of breasts, distribution of hair, sexual anesthesia, thyroid disease and blood pressure.

CRITERIA OF ABNORMALITY

These cards were then sorted by one of us (W. C. A.) into three piles, designated sexually normal, sexually abnormal one plus, and sexually abnormal double plus. While this classification was being made the blood pressure record was covered up so that a mental bias might not enter into the decision in regard to the many borderline cases. These decisions were particularly difficult when the data were not as complete on all points as they should have been. As we shall see later, a few of the criteria on which this classification was based were probably not significant or valid.

A typical subject classed as sexually deficient would have to have one or more of the following points in her history or findings: irregular, painful, scanty, or very profuse menstruation; late onset of menstruation or early menopause; early ovariectomy or hysterectomy for ovarian disease or for fibroids; infantile uterus; undeveloped breasts; fibroids; pathologic overweight; masculine distribution of body and facial hair; mannishness; sexual anesthesia; thyroid disease.

Naturally, little importance could be attached to a history of nulliparity as it is so often voluntary or due to defects in the husband. When, however, a woman had had a large family this fact was used to discount somewhat any slight signs which she might have of hypogonadism. In a number of cases we were helped by having a record of the findings at operation.

Women whose pelvic disease seemed to be due to the effects of gonorrhea or of peritonitis following criminal abortions were generally classed with the normal unless there were some signs or symptoms pointing to preexistent ovarian dysfunction. Naturally, the classification of many of these cases was difficult, and certain facts which will be brought out toward the close of the paper suggest that for our normal standards we should have excluded all those with any type of pelvic trouble which could possibly have damaged the ovaries or their circulation.

THE CORRECTION OF THE DATA FOR DIFFERENCES IN AGE DISTRIBUTION

We had next to divide our data into groups according to the ages of the subjects. In order that these groups might not be too small for statistical purposes, we grouped together ages 16-29, 30-39, 40-49, and 50 and over. It would be obviously unfair to compare the blood pressures of any two groups of women unless we could correct in some way for differences in the age distributions. The need for such a correction might be avoided if we could always have equal numbers of persons of the same ages in the two groups studied, but that is gen-

erally difficult of attainment. We would rather find some way of using all our material and then correcting each mean by a factor based on differences in the age distributions of the particular group and a "standard" group. In order to secure this standard group we took the readings from 573 women who, according to the criteria listed in the preceding section, were normal sexually. These were divided into the

TABLE 1.—*Sexually Normal Group* *

	Age Groups								All Ages Together	
	16–29		30–39		40–49		50+			
Blood Pressure	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent
90 to 99	1	0.7	4	2.5	2	1.8	..	....	7	1.2
100 to 109	13	8.7	15	9.5	4	3.6	3	2.0	35	6.1
110 to 119	58	38.7	36	23.0	16	14.5	12	7.7	122	21.3
120 to 129	50	33.3	48	30.5	21	19.1	10	6.4	129	22.6
130 to 139	18	12.0	33	21.0	26	23.6	28	18.0	105	18.3
140 to 149	7	4.7	11	7.0	21	19.1	33	21.2	72	12.6
150 to 159	1	0.7	5	3.2	11	10.0	18	11.5	35	6.1
160 to 169	..	....	1	0.6	4	3.6	16	10.2	21	3.7
170 to 179	1	0.7	2	1.2	2	1.8	10	6.4	15	2.6
180 to 189	..	....	..	....	1	0.9	6	3.8	7	1.2
190 to 199	..	....	1	0.6	1	0.9	5	3.2	7	1.2
200 to 209	..	....	1	0.6	..	....	4	2.6	5	0.9
210 to 219	..	....	..	....	1	0.9	1	1.6	2	0.3
220 to 229	1	0.7	..	....	..	....	3	2.0	4	0.7
230 to 239	..	....	..	....	..	....	4	2.5	4	0.7
240 to 249	..	....	..	....	..	....	3	2.0	3	0.5
Total.....	150	26.0	157	27.4	110	19.2	156	27.3	573	
Mean.....	122.1		125.8		135.3		154.4		134.5	
S. D.	13.9		16.0		19.3		30.7		25.0	
P. E. of mean..	0.8		0.8		1.2		1.7		0.7	

Correction for weight: 134.5 × 0.995 = 133.8

Age and Weight Distribution

	Number		Thin			Normal			Stout		
				Per Cent			Per Cent			Per Cent	
Age Groups	Total	Per Cent	Number	Down	Across	Number	Down	Across	Number	Down	Across
16–29.....	142	26.0	43	38.0	30.3	84	26	59.0	15	14.7	10.7
30–39.....	150	28.0	31	27.0	20.7	98	30	65.0	21	20.6	14.3
40–49.....	107	19.7	20	17.5	18.7	66	20	62.0	21	20.6	19.3
50+.....	144	26.3	20	17.5	13.9	79	24	55.0	45	44.1	31.1
Total.....	543†		114	21.0		327	60.0		102	19.0	

* In this and the following tables, F. means frequency; S. D., standard deviation, and P. E., probable error.

† This number is less than the 573 in the table above because the weight and height were not given in some of the records. A similar discrepancy will be found in other tables in this paper.

four age groups and the distribution curves were studied. As will be noted, the blood pressures were divided into class intervals of 10 mm. each. Table 1 summarizes the results obtained.

Now when we get the mean of a particular distribution and wish to correct it for age differences we multiply it by a factor obtained by dividing the mean of the normal group by a mean obtained by adding together the products of the numbers in the different age groups of

the particular distribution and the corresponding means from the standard group of 573, and dividing by the total number in the particular distribution. In other words, we compare the mean of the standard group with the weighted mean of a theoretical group in which the pressures are standard but the age distribution different. The method is simply an adaptation of one used in standardizing death rates.[8] The arithmetic of the process will be shown a little further on in the paper; this will doubtless make things clearer than any amount of description.

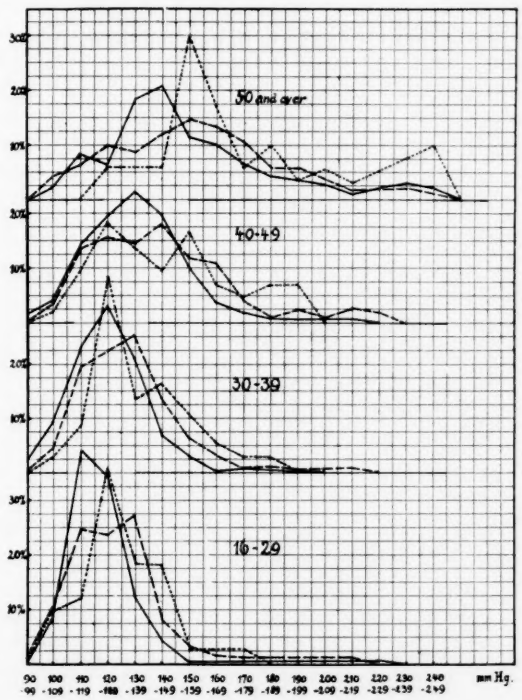

Chart 1.—Distribution curves for women at different ages: the solid line represents the sexually normal; the broken line, the sexually abnormal plus; and the dotted line, the sexually abnormal double plus.

STANDARDS OF NORMAL

In table 1 we note that the mean pressures for the four age groups are 122.1 ± 0.8; 125.8 ± 0.8, 135.3 ± 1.2, and 154.4 ± 1.7. If we remove from the 16 to 29 year group the data from eight women whose pelvic organs were questionable, the mean becomes 120.0 ± 0.5 and the

8. Pearl, R.: Introduction to Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1923, p. 198.

standard deviation 8.7 mm. If we remove from the 30 to the 39 group the readings from twelve women whose sexual status was similarly doubtful, that mean becomes 123.4 ± 0.8 and the standard deviation 13.9. These corrected figures are probably more trustworthy as standards of normal, but as it was impossible to arrive at definite and settled decisions as regards most of these borderline cases, we felt it best to abide by our first attempt at classification.

On turning to the last paper by one of us (W.C.A.), on the pressures of university freshmen, it will be noted that their readings averaged a little lower than those from the office patients here reported. The yearly means for the women between 16 and 30 ranged about 117, and for those between 30 and 40 they were about 119. These readings were taken, however, by the palpatory method which gives results from 5 to 10 mm. lower than those obtained with the auscultatory method. It appears, therefore, that the women coming to a physician's office whom we have classified as sexually normal have pressures at about the same level as those of their sisters attending the university.

It will be noted, again, that the normal pressure rises little in the twenties and thirties. The big rise comes in the forties and fifties. The rise in the mean with increasing age up to 40 seems to be due mainly to an upward shift of the mode, or peak of the distribution curve (fig. 1). After that it is due partly to a shift in the mode, and partly to an increase in the number of individuals with pathologic pressures. The increase in pathologic pressures is most striking in the women over 50.

THE CORRECTION OF THE DATA FOR DIFFERENCES IN WEIGHT

The need for an age correction factor in comparing the pressures of any two groups of women is obvious. The need for a correction factor for weight was not so obvious until we had prepared table 2. Then it became clear that it would be impossible to estimate the effect, let us say, of child-bearing on blood pressure, unless we could exclude the influence of the gain in weight which so often comes with pregnancy and lactation. We would either have to study a group of mothers who had preserved their anteparous weight or else we would have to use a correction factor for weight.

Symonds [9] has published extensive tables showing the relation between blood pressure, age, and weight but like all the insurance statistics they have little significance for the clinician because they are based on the findings in a group of men and women who have been selected as conforming to certain already chosen standards. In other

9. Symonds, B.: The Blood Pressure of Healthy Men and Women, Proc. A. Life Ins. Dir. of America **9**:22, 1922.

words, the statistics are based only on the data from accepted risks, and the examiner, having fixed the range, practically fixes the means that later he presents to us as standards of normal. The clinician would be helped more if the insurance men would publish the data from all those whom they examine. Even then, we would not get a perfect sampling from the population because those who know that they have high pressures know the futility of applying for insurance.

Even the clinician at times succumbs to the temptation to exclude bothersome pathologic cases from his frequency distributions, but as it is impossible to know where to begin or where to stop in this deleting process, and as we want first to study disease as we find it, we have

TABLE 2.—*Standards for the Weight Correction*

	Age Groups															
	16–29			30–39			40–49			50+			All Ages			
Blood Pressure	Thin	Nor-mal	Stout	Thin	Nor-mal	Stout	Thin	Nor-mal	Stout	Thin	Nor-mal	Stout	Thin	Nor-mal	Stout	Total
90 to 99	1	..	..	3	3	..	2	..	..	..	..	..	6	3	..	9
100 to 109	15	13	2	5	15	2	3	5	1	..	4	1	23	37	6	66
110 to 119	30	53	7	22	35	9	12	22	3	5	9	2	69	119	21	209
120 to 129	23	45	16	23	61	13	8	28	9	5	13	3	59	147	41	247
130 to 139	19	30	11	15	50	12	11	28	9	7	20	7	52	128	39	219
140 to 149	3	16	4	3	27	7	5	33	10	4	21	13	15	97	34	146
150 to 159	1	3	1	6	12	3	2	19	8	2	24	17	11	58	29	98
160 to 169	..	3	..	2	5	1	4	11	6	4	16	12	10	35	19	64
170 to 179	..	2	1	1	3	1	..	5	5	3	10	7	4	20	14	38
180 to 189	..	..	..	..	2	1	..	2	3	1	9	8	1	13	12	26
190 to 199	..	..	..	..	..	2	..	5	1	..	2	7	..	7	10	17
200 to 209	..	1	..	..	..	..	..	..	1	1	8	3	1	9	4	14
210 to 219	..	1	..	1	..	1	..	3	2	..	2	2	1	6	5	12
220 to 229	..	..	..	..	..	..	..	..	1	..	1	1	..	1	2	3
230 to 239	..	..	..	..	..	..	..	1	..	..	5	1	..	6	1	7
240 to 249	..	..	..	..	..	..	..	..	..	..	3	4	..	3	4	7
Total.....	92	167	42	81	213	52	47	162	59	32	147	88	252	689	241	1182
Mean.....	120.7	126.3	128.3	126.9	129.8	136.0	128.5	141.4	151.3	143.6	157.3	166.6	127.0	137.5	149.6	137.7
S. D.....	11.7	16.6	12.9	18.7	16.1	22.8	17.7	23.5	26.3	22.9	32.0	28.3	18.3	25.1	28.8	25.9
P.E. of mean	0.8	0.9	1.3	1.4	0.7	2.1	1.7	1.2	2.3	2.7	1.7	2.2	0.8	0.6	1.2	0.5
Percentage..	30.5	55.5	14.0	23.5	61.5	15.0	17.5	60.5	22.0	12.0	55.0	33.0	21.3	58.1	20.6	

Mean of 915 under 50 = 131.6 ± 0.5. Mean of 647 under 40 = 127.7 ± 0.4.

thought it best, at least for the present, to chart and to use all the data obtained.

In making table 2 it would probably have been better if we could have used only the data from the same sexually normal group which we used for the age standards, but that group, when divided into twelve parts, was hardly sufficient, and so we have used the data from 1,182 histories in which the record was full enough so that we could classify the individual as thin, normal or stout. The arithmetic involved in using the means of these smaller age and weight groups to correct the mean of a special distribution will be shown a little further on in the section on single and married.

In the larger distributions such as those of the "sexually abnormal" and those with abnormal hair or fibroids, we used the data in this table

to correct for age and for weight at the same time, but in the smaller groups we did not attempt to make the twelvefold classification and used instead a threefold one of thin, normal and stout. We then used in the calculation the means 127.0, 137.5 and 149.6, which are to be found in table 2; the age correction factor was obtained separately.

We see from these figures that the mean blood pressure increases 10 mm. as we pass from the thin to the normal and another 12 mm. as we pass from the normal to the stout. This is shown more graphically in figure 2. There it will be noted that in thin persons the big rise in blood pressure takes place late, that is, after 50. In the well proportioned and in the stout the rise is definite in the forties.

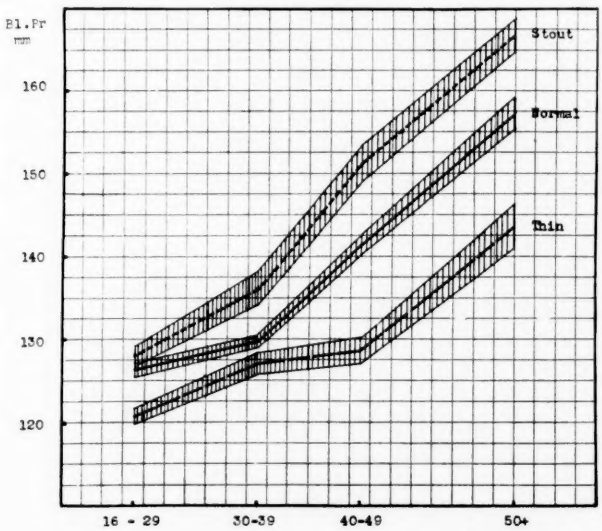

Chart 2.—Mean systolic blood pressure in women with different builds and ages: the shaded area represents the ± probable error of the mean.

The percentage composition of the different age groups according to weight, as shown at the lower end of table 2, is also of interest. As we all know, the weight of women tends to rise as they grow older. The percentage of well proportioned women seems to remain about the same from youth to old age.

SINGLE AND MARRIED

We next grouped the readings from single and married, the married including also the widowed, the divorced and the separated. Our idea was that a good many women might perhaps stay single because of sex deficiencies, mental and physical, and in that case we should, according

to our theory, find a greater number of high pressures among the single.

Table 3 and figure 3 show the number of single and married in the different age groups. It will be noted from table 4 that 23.4 per cent of the sexually normal were single, and on turning to the 1920 census report, we find that 23.9 per cent of the women in California over 15 are single. Apparently, then, our group of normals is fairly representative of California women.

TABLE 3.—*Single and Married*

	25-29 Years				30-39 Years				40-49 Years					
	Single		Married		Single		Married		Single		Married			
Pressure Blood	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	All Single	All Married
90 to 99	..	....	..	....	1	1.5	4	1.5	..	....	2	1.0	1	6
100 to 109	6	9.0	8	8.0	5	5.3	19	7.4	..	....	11	5.0	11	38
110 to 119	16	24.0	37	37.0	17	18.0	48	18.7	9	16.3	27	12.2	42	112
120 to 129	23	34.0	22	22.0	23	24.5	76	29.5	12	21.8	35	15.9	58	133
130 to 139	14	21.0	23	23.0	23	24.5	54	21.0	13	23.6	36	16.4	50	113
140 to 149	6	9.0	5	5.0	14	14.7	27	11.0	8	14.5	39	17.7	28	71
150 to 159	1	1.5	3	3.0	4	4.1	16	6.5	8	14.5	25	11.3	13	44
160 to 169	1	1.5	..	....	4	4.1	4	1.5	..	....	20	9.1	5	24
170 to 179	..	....	2	2.0	1	1.5	4	1.5	2	2.7	8	3.6	3	14
180 to 189	..	....	..	....	1	1.5	2	0.8	..	....	4	1.8	1	6
190 to 199	..	....	..	....	1	1.5	..	....	2	2.7	3	1.3	3	3
200 to 209	..	....	..	....	..	....	1	0.4	1	1.8	3	1.3	1	4
210 to 219	..	....	..	....	..	....	2	0.8	..	....	4	1.8	..	6
220 to 229	..	....	..	....	..	....	..	....	..	....	2	1.0	..	2
230 to 239	..	....	..	....	..	....	..	....	..	....	..	....	..	..
240 to 249	..	....	..	....	..	....	..	....	..	....	1	0.5	..	1
Total.....	67		100		94		257		55		220		216	577
Mean.....	125.3		124.4		131.7		129.6		138.3		142.3		131.3	133.5
S. D.....	12.4		13.8		17.5		18.3		20.6		26.0		17.7	22.0
P. E. of mean	1.0		0.9		1.2		0.7		1.9		1.2		0.8	0.6

Correction for age and weight: Single: $131.3 \pm 0.8 \times 1.006 = 132.1 \pm 0.8$
Married: $133.5 \pm 0.6 \times 0.984 = 131.4 \pm 0.6$

TABLE 4.—*Percentages of Single, Married and Divorced*

	Normal			Abnormal						Total	
				+			++				
		Per Cent			Per Cent			Per Cent			
	Number	Down	Across	Number	Down	Across	Number	Down	Across	Number	Per Cent
Single.....	134	23.4	40.3	146	28.0	44.2	52	36.0	15.5	332	27
Married and widowed...	412	72.0	48.7	347	68.0	41.0	86	60.0	10.3	845	69
Divorced and separated	27	4.6	54.0	17	4.0	34.0	6	4.0	12.0	50	4
Total.....	573		46.8	510		41.7	144		11.5	1227	

When we divided the single and married groups each into three other groups according to our classification into sexually normal and abnormal, we found, as we expected, that there were many more single among the abnormals, especially in the earlier years. Most of the abnormals seem ultimately to get married, but they have to wait until their more sexual sisters have taken their pick of the available men.

Table 3 shows the distribution of the pressures in married and single women between the ages of 25 and 49. Women under 25 were excluded from consideration because one does not question a woman's being single in the years before that. We note, however, in the United States census report for 1920 that more than 70 per cent of the women in California are married by the time they are 25. We have excluded the women over 50 because most of them have had the menopause by that time and we would not expect to find a sexual factor still operative.

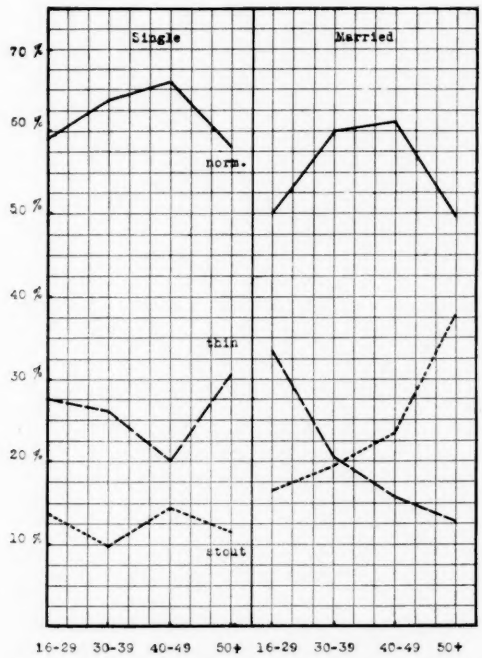

Chart 3.—Percentage of thin, normal and stout women, single and married, and at different ages.

When the two sets of distributions in table 3 are charted the curves show no definite differences. The mean of all the single women was 131.3 ± 0.8, and of the married women 133.5 ± 0.6. We note, however, in table 5 that there were nearly twice as many stout women among the married as there were among the single, so some correction had to be made for that. At the same time correction had to be made for the age differences. The arithmetic of the process is shown in the work sheet appended to the table.

TABLE 5.—*Body Build in Single and Married*

	Single							Married					
		Thin		Normal		Stout			Thin		Normal		Stout	
Age Groups	Total	Number	Per Cent	Number	Per Cent	Number	Per Cent	Total	Number	Per Cent	Number	Per Cent	Number	Per Cent
25-29	65	21	32.3	37	57.0	7	10.7	101	27	26.7	57	56.4	17	16.9
30-39	82	20	24.4	54	66.0	8	9.6	261	45	17.2	166	63.6	50	19.2
40-49	51	11	21.5	30	59.0	10	19.5	215	32	14.9	131	61.0	52	24.1
Total.....	198	52	26.2	121	61.1	25	12.7	577	104	18.0	354	61.4	119	20.6

	Married			
	No Children		With Children	
Build	Number	Per Cent	Number	Per Cent
Thin.....	40	21.6 ± 2.0	113	20.0 ± 1.1
Normal.....	112	60.5 ± 2.4	302	53.5 ± 1.4
Stout.....	33	17.9 ± 1.9	150	26.5 ± 1.3

Appendix
To Correct for Age and Weight

Single

Age	Thin		Normal		Stout		Total	
25-29	$21 \times 120.7 = 2534.7$		$37 \times 126.3 = 4673.1$		$7 \times 128.3 = 898.1$		52	6486.2
30-39	$20 \times 126.9 = 2538.0$		$54 \times 129.8 = 7009.2$		$8 \times 136.0 = 1088.0$		121	15924.5
40-49	$11 \times 128.5 = 1413.5$		$30 \times 141.4 = 4242.2$		$10 \times 151.3 = 1513.0$		25	3499.1
	52	6486.2	121	15924.5	25	3499.1	198	25909.8

$$\frac{25909.8}{198} = 130.8$$

Normal mean from table 2, age 16-49 = 131.6

$$\frac{131.6}{130.8} = 1.006 = \text{correction factor}$$

Married

Age	Thin		Normal		Stout		Total	
25-29	$27 \times 120.7 = 3258.9$		$57 \times 126.3 = 7199.1$		$17 \times 128.3 = 2181.1$		104	13081.4
30-39	$45 \times 126.9 = 5710.5$		$166 \times 129.8 = 21546.8$		$50 \times 136.0 = 6800.0$		354	47269.3
40-49	$32 \times 128.5 = 4112.0$		$131 \times 141.4 = 18523.4$		$52 \times 151.3 = 7867.6$		119	16848.7
	104	13081.4	354	47269.3	119	16848.7	577	77199.4

$$\frac{77199.4}{577} = 133.8$$

$$\frac{131.6}{133.8} = 0.984 = \text{correction factor}$$

$131.3 \pm 0.8 \times 1.006 = 132.1 \pm 0.8 =$ corrected mean of the single
$133.5 \pm 0.6 \times 0.984 = 131.4 \pm 0.6 =$ corrected mean of the married

We see then, as we expected, that the pressures of the single women average a little higher than those of the married women. The difference is so small that if we did not know that there is more hypogonadism among the single, and that the hypogonads have definitely higher pressures, we would pay no attention to it. Ordinarily, we put little confidence in a difference unless it is three or four times its probable error. That figure is obtained as follows:

$$132.1 \pm 0.8 - 131.4 \pm 0.6 = 0.7 \pm \sqrt{0.8^2 + 0.6^2} = 0.7 \pm 1.$$

In this case the difference is actually less than its probable error.[10]

TABLE 6.—*Sexually Abnormal* +

	Age Groups								All Ages Together	
	16-29		30-39		40-49		50+			
Blood Pressure	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent
90 to 99	1	0.7	1	0.6	1	0.8	..	....	3	0.6
100 to 109	14	10.2	7	4.3	4	3.4	4	4.3	29	5.7
110 to 119	33	24.2	32	19.7	17	14.3	6	6.5	88	17.2
120 to 129	32	23.4	36	22.4	18	15.2	9	9.8	95	18.7
130 to 139	37	27.0	40	25.0	17	14.3	8	8.7	102	20.0
140 to 149	11	8.0	22	13.7	21	17.7	11	12.0	65	12.7
150 to 159	5	3.6	11	6.8	14	11.8	13	14.1	43	8.5
160 to 169	2	1.5	5	3.1	13	10.7	12	13.1	32	6.3
170 to 179	1	0.7	2	1.2	5	4.2	10	10.9	18	3.5
180 to 189	..	....	2	1.2	1	0.8	6	6.5	9	1.8
190 to 199	..	....	1	0.6	2	1.7	6	6.5	9	1.8
200 to 209	..	....	..	....	1	0.8	3	3.7	4	0.8
210 to 219	1	0.7	2	1.2	3	2.5	1	1.1	7	1.4
220 to 229	..	....	..	....	2	1.7	..	....	2	0.4
230 to 239	..	....	..	....	..	....	2	2.1	2	0.4
240 to 249	..	....	..	....	..	....	1	1.1	1	0.2
Total.....	137	27.0	161	31.6	119	23.4	92	18.0	509	
Mean.....	126.8		132.9		143.4		156.8		138.1	
S. D.	16.0		19.2		26.2		30.1		20.7	
P. E. of mean..	0.9		1.0		1.6		2.1		0.6	

Correction for age and weight: All ages: $138.1 \pm 0.6 \times 1.007 = 139.1 \pm 0.6$

	Number		Thin			Normal			Stout		
				Per Cent			Per Cent			Per Cent	
Age Groups	Total	Per Cent	Number	Down	Across	Number	Down	Across	Number	Down	Across
16-29.....	131	27	29	33.3	22.1	79	26.7	60.3	23	22.0	17.6
30-39.....	155	32	33	38.0	21.3	92	31.0	59.4	30	28.5	19.3
40-49.....	117	24	17	19.5	14.5	79	26.7	67.5	21	20.0	18.0
50+.....	85	17	8	9.2	9.4	46	15.6	54.0	31	29.5	36.5
Total.....	488		87	17.6		296	60.6		105	21.8	

Figure 3 shows graphically the percentage of thin, normal and stout in all the women over 16, single and married. The striking difference between the two groups is to be found in the greater number of stout among the married women and particularly among the older married women. It is interesting to note also that the single women tend to get thin after 50 while their married sisters are getting fat. Apparently

10. Pearl (Footnote 8, p. 218).

the cartoonist's picture of the thin old maid rests on a firm biologic basis.

When we divide the group of married women into those who have had children and those who have not, we find, as we would expect, that 26.5 ± 1.3 per cent of the child-bearing group are stout as compared with 17.9 ± 1.9 per cent in the nulliparous group. We find also that even the childless married women are a little heavier than their single sisters, only 12.7 ± 1.6 per cent of whom are stout.

TABLE 7.—*Sexually Abnormal* + +

	Age Groups								All Ages Together	
	16-29		30-39		40-49		50+			
Blood Pressure	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent
90 to 99	..	....	..	....	..	....	..	....	..	....
100 to 109	3	9.1	1	2.8	1	2.3	..	....	5	3.5
110 to 119	4	12.2	3	8.3	4	9.3	..	....	11	7.7
120 to 129	12	36.5	13	36.0	8	18.6	2	6.6	35	24.6
130 to 139	6	18.2	5	13.9	6	14.0	..	....	17	12.0
140 to 149	6	18.2	6	16.7	4	9.3	2	6.6	18	12.7
150 to 159	1	3.0	4	11.1	7	16.3	9	30.0	21	14.7
160 to 169	..	....	2	5.6	3	7.0	5	16.7	10	7.0
170 to 179	1	3.0	1	2.8	2	4.6	2	6.6	6	4.2
180 to 189	..	....	1	2.8	3	7.0	3	10.0	7	4.9
190 to 199	..	....	..	....	3	7.0	1	3.3	4	2.8
200 to 209	..	....	..	....	..	....	2	6.6	2	1.4
210 to 219	..	....	..	....	1	2.3	1	3.3	2	1.4
220 to 229	..	....	..	....	..	....	..	....	..	....
230 to 239	..	....	..	....	..	....	..	....	..	....
240 to 249	..	....	..	....	1	2.3	3	10.0	4	2.8
Total.....	33	23.2	36	25.3	43	30.3	30	21.2	142	
Mean.....	129.0		136.4		150.3		173.5		146.8	
S. D.	13.9		17.8		33.6		31.4		29.3	
P. E. of mean..	1.6		1.9		3.4		3.8		1.7	

Correction for age and weight: All ages: 146.8 ± 1.7 × 0.980 = 143.9 ± 1.7

	Number		Thin			Normal			Stout		
				Per Cent			Per Cent			Per Cent	
Age Groups	Total	Per Cent	Number	Down	Across	Number	Down	Across	Number	Down	Across
16-29.....	29	21	6	33.3	20.7	16	20	55.0	7	17.0	24.3
30-39.....	35	25	6	33.3	17.1	24	30	68.6	5	12.2	14.4
40-49.....	43	31	3	16.7	7.0	24	30	56.0	16	39.0	37.0
50+	32	23	3	16.7	9.4	16	20	50.0	13	31.8	40.6
Total.....	139		18	13.0		80	57.5		41	29.5	

THE SEXUALLY ABNORMAL

In tables 6 and 7 we have analyzed the data from the women designated sexually abnormal, plus and double plus. As already pointed out, the first group contains the data from many doubtful cases in which it was hard to say where the line should be drawn. The second group is made up of women who were decidedly abnormal sexually. Figure 1 shows the distribution curves plotted from the data in tables 1, 6 and 7. These curves show the homogeneity of the data from the

younger women, the gradual shifting of the mode with age, and the marked spreading to the right in the later years. They show also the shifting of the whole distribution to the right (higher pressures) as we pass from the normal to the plus and again to the double plus.

After correcting the means of the plus and double plus groups for age and weight, we find that they are 139.1 ± 0.6 mm. and 143.9 ± 1.7 mm., respectively. As we expected, these figures are much higher than that for the normals, which, as will be remembered, was 133.8 ± 0.7 mm. The differences here are so much larger than their probable errors that the chances are hundreds of millions to one that they mean something.

TABLE 8.—*Age Distribution of the Different Groups*

	All Together		Normal		Sexually Abnormal +		Sexually Abnormal ++		Fibroids		Masculine Hair Distribution	
Age Groups	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
16-29	320	26.2 ± 0.3	150	26.1 ± 1.2	137	27.0 ± 1.3	33	23.2 ± 2.4	11	8.8 ± 1.7	65	36.3 ± 2.4
30-39	354	28.8 ± 0.3	157	27.4 ± 1.3	161	31.6 ± 1.4	36	25.3 ± 2.5	39	31.2 ± 2.8	58	32.4 ± 2.4
40-49	272	22.2 ± 0.3	110	19.2 ± 1.1	119	23.4 ± 1.3	43	30.3 ± 2.6	48	38.4 ± 2.9	38	21.2 ± 2.1
50+	278	22.8 ± 0.3	156	27.3 ± 1.3	92	18.0 ± 1.1	30	21.2 ± 2.3	27	21.6 ± 2.5	18	10.1 ± 1.5
Total	1,224		573	46.8 ± 0.3	509	41.6 ± 0.3	142	11.6 ± 0.2	125	10.2 ± 0.2	179	14.6 ± 0.2

	Ovariectomy		Hysterectomy		Thyroid Small		Thyroid Slightly Enlarged		Thyroid Definitely Enlarged and Toxic	
Age Groups	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
16-39	44	50.1 ± 3.6	13	25.6 ± 4.2	246	55.0 ± 1.6	83	71.0 ± 2.8	42	53.0 ± 3.8
50+	43	49.9 ± 3.6	38	74.4 ± 4.2	202	45.0 ± 1.6	34	29.0 ± 2.8	37	47.0 ± 3.8
Total.....	87	7.1 ± 0.5	51	4.1 ± 0.4	448	36.6 ± 0.3	117	9.6 ± 0.6	79	6.4 ± 0.5

The next problem is to study separately the influence of the different forms of abnormality which we have lumped together as "sexually abnormal." As we shall see, some seem to have a marked effect on the blood pressure and others do not.

MASCULINE DISTRIBUTION OF BODY HAIR

On turning to table 9 we note that there were 179 cases in which this bodily peculiarity was mentioned in the records. Undoubtedly there were many more in which such hair was present in moderate amount and not commented on. As we shall note again later when we come to study figure 4, there is a strange absence of the older women from this group. Most of those observed with a pronouncedly masculine distribution of hair, especially on the abdomen, were in their twenties. It would seem either that such hair must fall out later or else that a considerable number of these women must die young.

There was an incidence of 14.6 ± 0.7 per cent for the whole group of 1,224. Studies that we hope to report later indicate that this peculiarity is found mainly in women who have an infantile type of uterus. There were eighteen women in the group with that type of uterus, and ten of them, or 56 ± 8 per cent had an abnormal distribution of hair. In the combined plus and double plus groups the incidence was 26.3 ± 1.2 per cent.

TABLE 9.—*Masculine Distribution of Body Hair*

	Age Groups								All Ages Together	
	16–29		30–39		40–49		50+			
Blood Pressure	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent
90 to 99	..	....	..	....	1	2.6	..	....	1	0.6
100 to 109	7	10.8	1	1.7	1	2.6	..	....	9	5.0
110 to 119	17	26.1	10	17.3	5	13.1	2	11.1	34	19.0
120 to 129	20	30.8	17	29.3	5	13.1	2	11.1	44	24.5
130 to 139	11	16.9	14	24.1	10	26.3	2	11.1	37	20.6
140 to 149	6	9.2	6	10.3	7	18.4	2	11.1	21	11.7
150 to 159	1	1.5	5	8.6	2	5.3	3	16.7	11	6.1
160 to 169	2	3.1	3	5.2	3	7.9	1	5.5	9	5.0
170 to 179	1	1.5	..	....	..	....	1	5.5	2	1.1
180 to 189	..	....	..	....	1	2.6	1	5.5	2	1.1
190 to 199	..	....	1	1.7	2	5.3	1	5.5	4	2.2
200 to 209	..	....	..	....	..	....	2	11.1	2	1.1
210 to 219	..	....	1	1.7	1	2.6	..	....	2	1.1
220 to 229	..	....	..	....	..	....	..	....	..	....
230 to 239	..	....	..	....	..	....	1	5.5	1	0.6
240 to 249	..	....	..	....	..	....	..	....	..	....
Total.....	65	36.3	58	32.4	38	21.1	18	10.1	179	
Mean.....	125.7		134.3		140.5		158.9		135.0	
S. D.	14.9		19.4		25.1		33.4		23.2	
P. E. of mean..	1.3		1.7		2.8		5.3		1.2	

Correction for age and weight: All ages: $135.0 \pm 1.2 \times 1.030 = 139.1 \pm 1.2$

	Number		Thin			Normal			Stout		
				Per Cent			Per Cent			Per Cent	
Age Groups	Total	Per Cent	Number	Down	Across	Number	Down	Across	Number	Down	Across
16-29.....	63	36.6	22	58.0	35.0	28	30.8	44.5	13	30.3	20.5
30-39.....	58	33.8	11	29.0	19.0	35	38.5	60.4	12	28.0	20.6
40-49.....	36	20.9	4	10.5	11.1	21	22.8	58.3	11	25.6	30.6
50+.....	15	8.7	1	2.5	6.7	7	7.9	46.7	7	16.1	46.7
Total.....	172		38	22.0		91	53.0		43	25.0	

It may easily be that in some of the cases the abnormal hairiness was due not so much to a deficiency in the ovarian secretion which restrains growth as to an oversupply of some factor that promotes growth. The fathers of a good many of these women were particularly hairy, and some of the daughters had unusually luxuriant growths of hair on the head, eyebrows, arms and legs. We have the impression, however, that in women, hairiness even on the arms and legs is a sign of hypogonadism. In a few cases the hairiness of the abdomen developed after a pelvic operation, but in no such case was it abundant.

Just as we would expect from our theory, these women whose ovarian development was so poor that a latent hairiness could emerge have high pressures. As will be seen from table 9, the mean was 139.0 ± 1.2 mm. Furthermore, if we plot the means for the four age groups, or if we plot the corresponding percentages with pressures over

TABLE 10.—*Fibroids*

	Age Groups								All Ages Fibroids Sure		All Ages (+ and ++) Fibroids Absent	
	16–29		30–39		40–49		50+					
Blood Pressure	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent	F.	Per Cent
90 to 99	..	....	..	....	..	....	..	....	..	....	3	0.9
100 to 109	..	....	1	2.5	1	2.1	1	3.7	3	2.4	16	4.6
110 to 119	1	9.1	5	12.8	3	6.3	1	3.7	10	8.0	62	17.9
120 to 129	6	54.6	13	33.3	9	18.8	3	11.1	31	24.8	56	16.2
130 to 139	2	18.2	10	25.6	6	12.5	2	7.4	20	16.0	76	21.9
140 to 149	2	18.2	5	12.8	9	18.8	2	7.4	18	14.4	41	11.8
150 to 159	..	....	2	5.1	6	12.5	7	26.0	15	12.0	33	9.5
160 to 169	..	....	2	5.1	5	10.4	4	14.8	11	8.8	19	5.5
170 to 179	..	....	1	2.5	4	8.3	3	11.1	8	6.4	11	3.2
180 to 189	..	....	..	....	..	....	1	3.7	1	0.8	10	2.9
190 to 199	..	....	..	....	2	4.2	1	3.7	3	2.4	6	1.7
200 to 209	..	....	..	....	1	2.1	..	....	1	0.8	5	1.4
210 to 219	..	....	..	....	1	2.1	..	....	1	0.8	6	1.7
220 to 229	..	....	..	....	..	....	..	....	..	....	..	....
230 to 239	..	....	..	....	..	....	..	....	..	....	..	....
240 to 249	..	....	..	....	1	2.1	2	7.4	3	2.4	3	0.9
Total	11	8.8	39	31.2	48	38.4	27	21.1	125	....	347	....
Mean	129.0		132.7		149.5		158.5		144.4		139.5	
S. D.	8.9		15.0		27.8		32.0		26.6		26.2	
P. E. of mean	1.8		1.6		2.7		4.1		1.6		0.9	

Correction for age and weight: Fibroids (all ages): $144.4 \pm 1.6 \times 0.983 = 142.0 \pm 1.6$
No fibroids (all ages): $139.5 \pm 0.9 \times 0.983 = 137.1 \pm 0.9$

Age and Weight Distribution
Fibroids

Age Groups	Total		Thin		Normal		Stout	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
16–29	19	9.3	7	36.8	9	47.3	3	15.9
30–39	63	30.8	20	31.7	34	54.0	9	14.3
40–49	80	39.2	10	12.5	55	69.0	15	18.5
50+	42	20.6	4	9.5	23	55.0	15	35.5
Total	204	....	41	20.0	121	59.3	42	20.7
				No Fibroids				
16–29	121	33.3	30	24.8	70	58.0	21	17.2
30–39	110	30.2	26	23.5	66	60.0	18	16.5
40–49	69	19.0	13	18.9	37	53.6	19	27.5
50+	64	17.6	4	6.3	37	57.8	23	35.9
Total	364	....	73	20.0	210	57.7	81	22.3

130 or 140 mm., we see that the big difference between the normal and the hairy comes in the early years, and particularly in the thirties. After 50 there is little difference between the two groups. We find the same thing when we compare the data from the "normals" and the "one plus," and we will see it again when we come to analyze Plummer's figures on hyperplastic and nonhyperplastic goiter. With fibroids, the

big difference is found, as we might have expected, in the forties. Strange to say, in the "double plus" group the pressures continue to rise even in the fifties.

WOMEN WITH A FIBROTIC OR DEFINITELY FIBROID UTERUS

Table 10 shows the distribution of the data from these women. The high corrected mean, 142.0 ± 1.6, indicates that these tumors have something to do with the production of hypertension. It may be, however, that in some cases the evenly enlarged fibrotic type of uterus is the result of hypertension and not its cause; or, more probably, they are both the result of some underlying diathesis.

As already pointed out, the greatest difference between the pressures of the normal and the fibrotic comes in the forties when the means are 135.3 ± 1.2 and 149.5 ± 2.7, respectively.

Polak, Mittell and McGrath [11] once attempted to correlate hypertension and fibroid disease but as they did not use modern statistical methods and did not publish their frequency distributions it is impossible now to say what they got.

WOMEN WITH THYROID DISEASE

Table 11 gives a summary of the data from the women in the plus and double plus groups who had (1) no apparent thyroid disease; (2) who had somewhat enlarged thyroids, and (3) who had large or toxic thyroids. Unfortunately, some of the groups are pretty small, in spite of the fact that we grouped together women in ages 16-39 and 40-70.

The figures show that although the women with thyroid disease had pressures averaging considerably higher than normal, in the "sexually abnormal" group there was no significant difference between the pressures of those with and without thyroid disease. In a large proportion of the cases of thyroid disease the women had to be placed in the sexually abnormal group on account of severe disturbance of menstruation, pelvic disease, sexual anesthesia, etc. Doubtless the difference between the pressures of the normal and the plus group would have been more marked if we had not included with the latter so many women with enlarged but comparatively innocuous thyroids.

Fortunately, we have at our disposal Plummer's excellent study of the pressures in 1,728 women with nonhyperplastic goiter and 833 with hyperplastic goiter.[12] He does not give the data that would enable us to make the correction for weight but we can make the necessary

11. Polak, J. O.; Mittell, E. A., and McGrath, A. B.: What Is the Relation of Hypertension to Fibroid Disease of the Uterus? Am. J. Obst. & Gynec. **4**:227 (Sept.) 1922.

12. Plummer, H. S.: Blood Pressure and Thyrotoxicosis, Tr. A. Am. Phys. **30**:450, 1915.

correction for age. The corrected mean for the nonhyperplastic is 137.3, and for the hyperplastic, 151.0 mm. If the latter figure were corrected for weight, it would doubtless be still higher. As we have already noted in the section on abnormal hairiness, the big difference comes in the earlier years.

TABLE 11.—*Thyroid Disease*

All cases taken from the plus and double plus groups

Blood Pressure	Thyroid Small 16-39 F	Thyroid Small 40-50+ F	Thyroid Somewhat Enlarged 16-39 F.	Thyroid Somewhat Enlarged 40-50+ F.	Thyroid Definitely Enlarged or Big and Toxic 16-39 F.	Thyroid Definitely Enlarged or Big and Toxic 40-50+ F.	All Ages Thyroid Not Enlarged	All Ages Thyroid Somewhat Enlarged	All Ages Thyroid Big and Toxic
From 90 to 99	1	1	1	.	..	..	2	1	..
100 to 109	16	7	6	1	2	..	23	7	2
110 to 119	51	21	17	4	7	5	72	21	12
120 to 129	61	23	20	4	13	6	84	24	19
130 to 139	64	24	17	4	9	4	88	21	13
140 to 149	27	30	8	2	8	2	57	10	10
150 to 159	9	32	9	5	3	6	41	14	9
160 to 169	8	27	2	2	..	5	35	4	5
170 to 179	3	8	2	4	..	3	11	6	3
180 to 189	4	7	..	4	..	1	11	4	1
190 to 199	..	6	..	2	..	3	6	2	3
200 to 209	..	6	..	..	..	..	6	..	..
210 to 219	2	4	1	1	..	1	6	2	1
220 to 229	..	1	..	1	..	..	1	1	..
230 to 239	..	1	..	..	..	1	1	..	1
240 to 249	..	4	..	..	..	..	4	..	..
Total	246	202	83	34	42	37	448	117	79
Mean	130.6	150.6	131.1	154.5	130.0	152.3	139.5	137.9	140.5
S. D.	18.0	29.9	19.2	30.4	13.0	29.6	26.0	25.4	25.0
P. E. of mean	0.8	1.4	1.4	3.5	1.3	1.3	0.8	1.5	1.8

Correction for age and weight:

Thyroid normal: $139.5 \pm 0.8 \times 1.005 \times 0.995 = 139.5 \pm 0.8$

Thyroid somewhat enlarged: $137.9 \pm 1.5 \times 1.032 \times 1.002 = 142.6 \pm 1.5$

Thyroid big and toxic: $140.5 \pm 1.8 \times 1.001 \times 0.994 = 139.8 \pm 1.8$

Age Groups	Number Total	Number Per Cent	Thyroid Small: Thin Number	Thin Per Cent Down	Thin Per Cent Across	Normal Number	Normal Per Cent Down	Normal Per Cent Across	Stout Number	Stout Per Cent Down	Stout Per Cent Across
16-39	216	52.5	50	69.5	23.1	126	52.0	58.4	40	41.3	18.5
40-50+	195	47.5	22	30.5	11.3	116	48.0	59.5	57	58.7	29.2
Total	411		72	17.5		242	59.0		97	23.5	
Thyroid Palpable or Slightly Enlarged											
16-39	91	62.0	24	75.0	26.5	53	59.0	58.0	14	56.0	15.5
40-50+	56	38.0	8	25.0	14.3	37	41.0	66.0	11	44.0	19.7
Total	147		32	21.8		90	61.2		25	17.0	
Thyroid Definitely Enlarged or Big and Toxic											
16-39	42	53.0	11	65.0	26.2	20	49.0	47.6	11	52.5	26.2
40-50+	37	47.0	6	35.0	16.0	21	51.0	57.0	10	47.5	27.0
Total	79		17	21.5		41	52.0		21	26.5	

We had some eighteen women with hypothyroidism, most of whom showed very high pressures. Their data are not tabulated here because of the smallness of the group. The fact that both hypothyroidism and hyperthyroidism are associated with hypertension shows that the increase

in pressure is due, not to changes in the amount of thyroxin, but to the primary disturbance which damages the gland one way or the other.

WOMEN WITH ABNORMAL MENSTRUATION

It is hard to deal with the group with abnormal menstruation statistically because so many have difficulties in youth and no trouble later. Some begin to menstruate late; some have pain; some are irregular;

TABLE 12.—*Menstruation*

Blood Pressure	Normal Menstruation		Abnormal Menstruation		Age 16-39	
	Age 16-29 F.	Age 30-39 F.	Age 16-29 F	Age 30-39 F.	Normal	Abnormal
From 90 to 99	1	3	1	3	4	4
100 to 109	12	8	12	12	20	24
110 to 119	39	22	41	32	61	73
120 to 129	35	47	45	30	82	75
130 to 139	24	36	31	33	60	64
140 to 149	6	22	14	13	28	27
150 to 159	4	13	1	6	17	7
160 to 169	1	2	1	5	3	6
170 to 179	1	2	1	2	3	3
180 to 189	..	1	..	..	1	..
190 to 199	..	1	..	..	1	..
200 to 209	..	1	..	..	1	..
210 to 219	..	1	..	..	1	..
220 to 229	..	..	..	..	..	..
230 to 239	..	..	..	..	..	..
240 to 249	..	..	..	..	..	..
Total	123	159	147	136	282	283
Mean	123.8	132.0	124.7	127.5	128.4	126.0
S. D.	13.4	18.5	12.7	16.3	17.0	14.6
P. E. of mean	0.8	1.0	0.7	0.9	0.7	0.6

Correction for age and weight: $128.4 \times 1.000 \times 0.997 = 128.0 \pm 0.7$
$126.0 \times 1.000 \times 1.003 = 126.5 \pm 0.6$

Age Groups	Number		Menstruation Normal								
			Thin			Normal			Stout		
			Number	Per Cent		Number	Per Cent		Number	Per Cent	
	Total	Per Cent		Down	Across		Down	Across		Down	Across
16-29	114	43.5	31	52.0	27.0	68	43.0	60.0	15	33.3	13.0
30-39	148	56.5	29	48.0	19.5	89	57.0	60.0	30	66.6	20.5
Total	262		60	22.9		157	60.0		45	17.1	
			Menstruation With Difficulties								
16-29	149	51.7	43	55.0	29.0	87	50.0	58.5	19	54.0	12.5
30-39	139	48.3	35	45.0	25.5	88	50.0	63.0	16	46.0	11.5
Total	288		78	27.0		175	61.0		35	12.0	

some flow too little, others too much; others have psychic disturbances. It seemed impracticable to deal with so many small groups so we put them all together as shown in table 12. With the hope of bringing out differences more clearly we took only the women under 40. It will be seen that there is no significant difference between the mean pressures of the two groups with normal and abnormal menstruation. It is only 1.5 ± 0.9 mm.

SEXUAL ANESTHESIA

There were only sixty-four cases in which we had a record of this defect. This figure naturally does not give any idea of the incidence of this trouble as questions were not asked unless signs of hypogonadism were marked. It will be noted in table 13 that the mean pressure was 140.5 ± 1.7 mm., which is decidedly abnormal.

OVARIECTOMY AND HYSTERECTOMY

Table 14 shows that the women who have had severe operations on their pelvic organs have pressures that average higher than normal (137.0 ± 2.2 and 139.5 ± 3.3). Our impression is that this increase is due not so much to the operation as to the conditions that called for

TABLE 13.—*Sexual Anesthesia*

Blood Pressure	Number	Per Cent	Blood Pressure	Number	Per Cent
From 90 to 99	..	....	From 170 to 179	1	1.6
100 to 109	5	7.8	180 to 189	1	1.6
110 to 119	7	11.0	190 to 199	..	....
120 to 129	15	23.4	200 to 209	1	1.6
130 to 139	15	23.4	210 to 219	..	....
140 to 149	11	17.2	220 to 229	..	....
150 to 159	3	4.7	230 to 239	..	....
160 to 169	5	7.8	240 to 249	..	....
Total				64	
Mean					135.1
S. D.					19.6
P. E. of mean					1.6

Correction for age and weight: 135.1 ± 1.6 × 1.040 × 1.000 = 140.5 ± 1.7

Age Groups	Number	Per Cent	Build	Number	Per Cent
16 to 29	25	39.0 ± 4.1	Thin	13	20.0 ± 3.4
30 to 39	15	23.5 ± 3.6	Normal	39	61.0 ± 4.1
40 to 49	20	31.0 ± 3.9	Stout	12	19.0 ± 3.3
50 and over	4	6.5 ± 2.0			

it. It seemed to be higher in those who had begun life with poor pelvic organs than in those who had acquired them by the gonorrheal route.

EFFECTS OF PREGNANCY

Table 15 shows that when we exclude the influence of age and weight there is no difference between the pressures of women who have and who have not been pregnant.

EARLY OR LATE MENOPAUSE

In table 16 we have divided the women of 50 years and over into two groups: one in which the menopause had occurred before 50, and the other in which it had either occurred after 50 or had not yet appeared. As will be seen, there is no significant difference between the mean pressures of the two groups.

We have records of two interesting women: one, aged 40, with a spontaneous menopause at 20 and a blood pressure of 110 systolic, 75 diastolic; the other is 27, with an operative menopause at 17 and a blood pressure of 134 systolic, 85 diastolic. Much apparently depends on the inheritance.

TABLE 14.—*Ovariectomy and Hysterectomy* *

Blood-Pressure	Ovariectomy		Hysterectomy		All Ages	
	Age 16-39 F.	Age 40-50+ F.	Age 16-39 F.	Age 40-50+ F.	Ovariectomy	Hysterectomy
From 90 to 99	..	..	..	..	..	..
100 to 109	5	3	..	2	8	2
110 to 119	13	1	4	5	14	9
120 to 129	12	6	3	5	18	8
130 to 139	5	7	3	1	12	4
140 to 149	5	7	2	6	12	8
150 to 159	1	5	.	9	6	9
160 to 169	..	4	..	2	4	2
170 to 179	1	3	1	1	4	2
180 to 189	1	2	..	2	3	2
190 to 199	..	3	..	1	3	1
200 to 209	..	..	..	..	..	..
210 to 219	1	1	..	..	2	..
220 to 229	..	..	..	..	..	..
230 to 239	..	..	..	1	..	1
240 to 249	..	1	..	3	1	3
Total	44	43	13	38	87	51
Mean	127.9	151.0	130.6	153.5	139.3	147.6
S. D.	21.5	29.5	16.4	37.4	27.6	34.8
P. E. of mean	2.1	3.0	1.5	4.1	2.2	3.3

Correction for age and weight: $139.3 \times 0.997 \times 0.987 = 137.0 \pm 2.2$
$147.6 \times 0.956 \times 0.989 = 139.5 \pm 3.3$

Ovariectomy (+ and ++)

Age Groups	Number		Thin			Normal			Stout		
	Total	Per Cent	Number	Per Cent Down	Per Cent Across	Number	Per Cent Down	Per Cent Across	Number	Per Cent Down	Per Cent Across
16-39	40	49.0	7	78.0	17.5	25	48.0	62.5	8	38.0	20.0
40-50+	42	51.0	2	22.0	48.0	27	52.0	64.0	13	62.0	31.0
Total	82		9	11.0		52	63.5		21	25.5	

Hysterectomy (+ and ++)

16-39	13	29.0	6	86.0	46.0	6	23.0	46.0	1	8.3	8.0
40-50+	32	71.0	1	14.0	3.1	20	77.0	62.5	11	91.7	34.4
Total	45		7	15.5		26	58.0		12	26.5	

* Ovariectomy includes removal of ovarian cysts; hysterectomy includes total and partial hysterectomy.

We had several opportunities to observe the big rise that, as is well known, sometimes appears at the menopause. One woman went from 155 to 200 mm.; another from 105 to 150; another from 145 to 205, and another from 160 to 220. We encountered a few cases, however, in which the pressure actually dropped during and after the change, and we saw many, of course, in which there was no striking change.

THE AGE COMPOSITION OF THE DIFFERENT GROUPS

Table 8 and figure 4 show us the age composition of the different groups that we have been studying, and from that we can get some idea of the time of life when the various disturbances or abnormalities appear. Thus, we are not surprised to find that most of the women in whom fibroids were discovered were in their thirties and forties, but we

TABLE 15.—*Pregnancy and Child-Bearing, All Ages*

Blood Pressure	No Children F.	No Children Per Cent	Children and Pregnancies F.	Children and Pregnancies Per Cent
From 90 to 99	1	0.5	6	1.0
100 to 109	11	5.8	30	5.3
110 to 119	37	19.7	89	15.7
120 to 129	42	22.3	102	18.0
130 to 139	35	18.6	98	17.3
140 to 149	21	11.2	81	14.3
150 to 159	13	6.9	57	10.0
160 to 169	12	4.4	29	5.1
170 to 179	5	2.6	22	3.9
180 to 189	5	2.6	14	2.5
190 to 199	2	1.1	6	1.0
200 to 209	..	....	14	2.5
210 to 219	1	0.5	7	1.2
220 to 229	1	0.5	4	0.8
230 to 239	..	....	4	0.8
240 to 249	2	1.1	4	0.8
Total	188		567	
Mean	135.9		140.8	
S. D.	25.7		27.9	
P. E. of mean	1.3		0.8	

Correction for age and weight: $135.9 \times 1.011 \times 1.003 = 137.8 \pm 1.3$ $140.8 \times 0.991 \times 0.992 = 138.4 \pm 0.8$

Age Groups	Total Number	Total Per Cent	No Children Number	No Children Per Cent Down	No Children Per Cent Across	Children and Pregnancies Number	Children and Pregnancies Per Cent Down	Children and Pregnancies Per Cent Across
16–29	132	17.5	46	24.5	34.8	86	15.2	65.1
30–39	235	31.2	55	29.2	23.5	180	31.7	76.5
40–49	181	24.0	50	26.6	27.5	131	23.1	72.5
50+	207	27.3	37	19.7	17.9	170	30.0	82.1
Total	755	....	188	25.0		567	75.0	
Build								
Thin	153	20.0	40	21.6	26.0	113	20.0	74.0
Normal	414	55.4	112	60.5	27.0	302	53.5	73.0
Stout	173	24.6	33	17.9	18.0	150	26.5	82.0
Total	750	....	185	25.0		565	75.0	

are puzzled to note that most of the women with a masculine distribution of body hair were under 30. What happens to them after that? Do they die or does the hair fall out? This is a question that will be of interest to the medical directors of life insurance companies.

We see that in the later years of life the curve for the sexually normal parallels that for all the women in California (fourteenth census, 1920). In the early twenties, when young bodies tend to be strong and well, an internist does not see a full representation from the women

in his community, but the quota is more than made up in the thirties. Strange to say, there does not seem to be any increase in the incidence of disease in the years after 50. Apparently when final disease and death come they disable these older people so swiftly that few of them are able to visit a downtown consultant.

It is hard to explain the marked difference in the age composition of the plus and the double plus groups. One has its high peak in the

TABLE 16.—*Menopause in Women Aged 50 and Over*

	Age			
	Below 49		50-59	
Blood Pressure	F.	Per Cent	F.	Per Cent
From 90 to 99	..	....	..	....
100 to 109	3	2.7	1	1.0
110 to 119	7	6.4	4	4.1
120 to 129	7	6.4	5	5.1
130 to 139	12	10.9	15	15.3
140 to 149	15	13.6	12	12.2
150 to 159	18	16.4	20	20.5
160 to 169	9	8.2	13	13.1
170 to 179	9	8.2	10	10.2
180 to 189	8	7.3	5	5.1
190 to 199	5	4.5	2	2.0
200 to 209	7	6.4	5	5.1
210 to 219	2	1.8	..	....
220 to 229	2	1.8	..	....
230 to 239	2	1.8	2	2.0
240 to 249	3	2.7	3	3.0
260+	1	0.9	1	1.0
Total	110	53.0	98	47.0
Mean	162.0		160.5	
S. D.	34.1		31.4	
P. E. of mean	2.1		2.2	

Correction for weight: $162.0 \times 1.001 = 162.2 \pm 2.1$
$160.5 \times 0.997 = 160.0 \pm 2.2$

	Number		Thin			Normal			Stout		
				Per Cent			Per Cent			Per Cent	
Age Groups	Total	Per Cent	Number	Down	Across	Number	Down	Across	Number	Down	Across
Menopause under 49	106	54.0	11	55.0	10.4	63	57.0	59.4	32	48.5	30.2
Menopause, 50 to 59	90	46.0	9	45.0	10.0	47	43.0	52.0	34	51.5	38.0
Total	196		20	10.2		110	56.0		66	33.8	

thirties and the other in the forties. The relatively small number of old women in both groups suggests a mortality rate higher than that for the normals, and that is probably the case. Their greater susceptibility to hypertension alone would give them a shorter expectancy of life. It might be noted here, however, that women seem to tolerate high pressures much better than men. Our impression is that they have fewer symptoms and that they live longer than men with similar pressures.

DIASTOLIC PRESSURE

In this paper we have confined our attention for the most part to a consideration of the systolic pressure because it seems to be the more interesting one. It is easier to measure and it has a wider range. The variations in the diastolic pressure are rather small as compared with the error inherent to the technic.

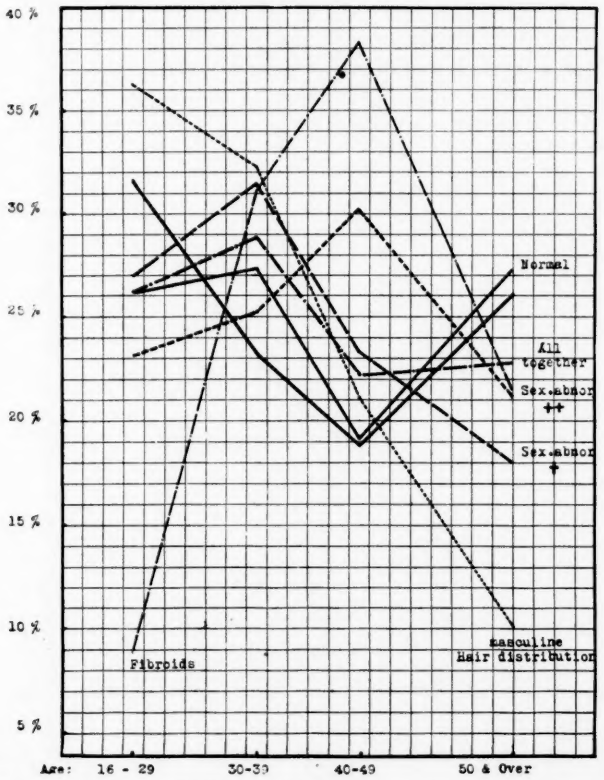

Chart 4.—Age distribution of the different groups of women studied: the double line represents the distribution of the women in California over 16.

Table 17 shows the distribution of the diastolic pressures in the normal and in the combined plus and double plus groups. The means are shown graphically in figure 5, and it will be seen that they are higher in the sexually abnormal just as the systolic pressures are. The difference between the two means is ten times its probable error, which makes it almost certainly significant in spite of the fact that we have not calculated age and weight corrections.

COMMENT

We have seen now that women with poor ovaries are likely, early in life, to develop hypertension. The next question is: Do they ever get it early when they have good ovaries? By early we mean in the years before 30. The answer is probably yes, and we will do well now and in the future to concentrate our attention on these exceptions to the rule. As Darwin once pointed out, we can learn more from the study of troublesome exceptions than from anything else, so we will turn back and review carefully the records of the women under 30 who had hypertension, but who, in the original classification, were placed with the normals. Before we do this we will analyze briefly a couple of interesting cases seen since the present work was begun.

TABLE 17.—*Diastolic Pressure in Normal, + and ++*

	Age 16-29		Age 30-39		Age 40-49		Age 50+		All Ages	
Blood Pressure	Normal F.	+ and ++ F.	Normal F.	+ and ++ F.	Normal F.	+ and ++ F.	Normal F.	+ and ++ F.	Normal	+ and ++
40 to 49	1	..	..	..	..	..	..	..	1	..
50 to 59	5	1	..	1	..	..	..	..	5	2
60 to 69	48	6	8	8	3	2	3	..	62	16
70 to 79	51	41	39	28	15	19	20	10	125	98
80 to 89	18	53	62	70	39	39	42	31	161	193
90 to 99	3	40	24	51	33	51	37	28	97	170
100 to 109	1	7	8	19	9	18	28	23	46	67
110 to 119	..	1	..	3	3	8	14	11	17	23
120 to 129	..	..	..	3	..	7	4	5	4	15
130 to 139	..	1	..	..	..	3	1	2	1	6
140 to 149	1	..	..	1	..	..	2	3	3	4
150+	..	..	..	..	..	..	..	3	..	3
Total.....	129	150	141	184	102	147	151	116	522	597
Mean.....	82.0	84.9	83.5	88.2	88.3	93.5	96.9	98.8	84.7	90.7
S. D.....	11.1	10.9	9.4	12.4	10.3	14.1	14.9	18.0	14.3	14.9
P. E. of mean	0.8	0.6	0.6	0.6	0.7	0.8	0.8	1.1	0.4	0.4

The first is that of a girl of 19, with a pressure of 250 systolic, 150 diastolic. She was apparently well until two months before she came to us, when she developed an acute glomerulonephritis, with nitrogen retention, pulse of 120, metabolism of plus 34 per cent, and a large heart. She was finely built, her pelvic organs seemed normal, and there was nothing to suggest a sexual abnormality unless the hyperthyroidism. Strange to say, there was no history of infection past or recent to account for the nephritis. There were no dead teeth; the tonsils were well removed at the age of 9, and the appendix was removed for slight symptoms nearly two years before our examination. The fact that as long as she can remember she has gotten up once or twice at night to urinate indicates that she has carried poor kidneys from early childhood or perhaps even from birth.

Another girl of 17 had a pressure of 220 systolic, 160 diastolic. She also had a nephritis with nitrogen retention, severe headache, ocular changes and dopiness. A brother died in childhood with the same condition. Again, there was no history of infection to explain the nephritis.

Mrs. C., aged 25, had a blood pressure of 220 systolic, 140 diastolic. She was finely built and sexual enough to have two illicit pregnancies at 19 and 20. Criminal abortions left her with considerable pelvic infection and probably a pus

tube. It is a question whether or not she should be placed with the normals. Our impression was that her ovaries were still normal and that, like the preceding two girls, she had the nephritic type of hypertension.

Miss G., aged 23, had a blood pressure of 178 systolic, 120 diastolic. She had inflammatory rheumatism at 19; dropsy at 12; a criminal abortion at 21, followed by some pelvic trouble and leukorrhea ever since; a big heart with a loud murmur and a large albuminuria. Here again we had a nephritic hypertension based on severe infectious damage in childhood. Her pelvic organs probably were damaged too.

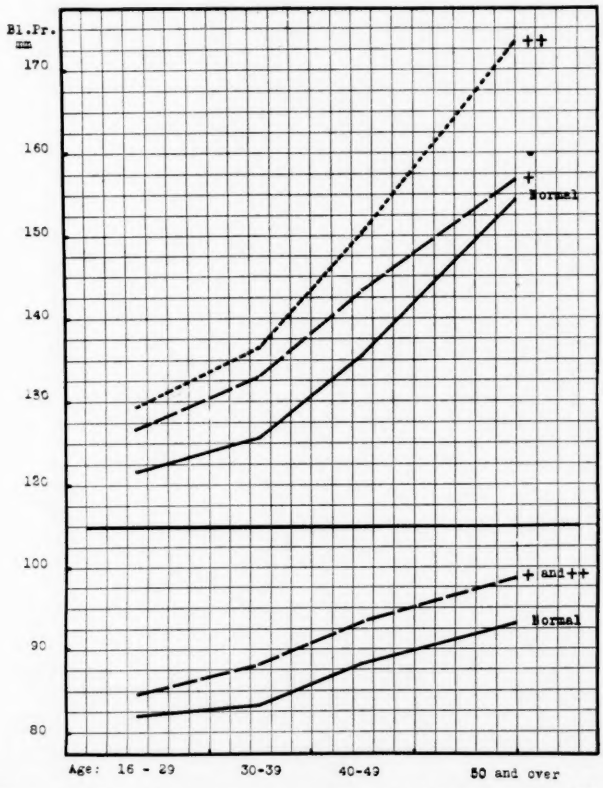

Chart 5.—Mean blood pressure, systolic and diastolic, at the different ages, and in the sexually normal and abnormal groups.

Mrs. B., aged 28, had a blood pressure of 150 systolic, 95 diastolic. Dr. T. Addis found a marked impairment of kidney function and she developed a pressure over 200 during pregnancy. Her physical development showed some male characteristics and it might easily have been that her ovaries were insufficient; but primarily she seemed to have renal arteriosclerosis.

If we turn now to a consideration of the seven women under 30 with pressures between 140 and 149, we find several whose ovaries may have been abnormal but who are certainly hard to classify. One had a double tubal pregnancy and

now has a questionable left ovary and some hyperthyroidism. Another has been irregular in her menstruation and is somewhat hypothyroid. Another has considerable arteriosclerosis; she flows to excess and has had curettements. Another when seen was dying with a huge liver filled with metastases from a carcinoma of the anal ring. The necropsy showed normal pelvic organs. Another had an anteflexed, retroposed uterus. In addition she was a nun. Another seemed to be normal except for painful menstruation. At 18 she was already having illicit sexual relations. The seventh, so far as we could see, was normal sexually.

The impression we get from all this is that when we find a blood pressure over 150 mm. in a well sexed woman under 30, it is probably not an essential hypertension, or hyperpiesis, but is due to a nephritis or arteriosclerosis. It seems probable that some of those with pressures between 130 and 150 have the primary type of hypertension in spite of the fact that they have normal pelvic organs, but more careful studies will have to be made on the individuals in this group. It may also be

TABLE 18.—*Summary*

	Corrected Mean
1,182 sexually normal and abnormal	137.7 ± 0.5
573 sexually normal	133.8 ± 0.7
509 sexually abnormal plus	139.1 ± 0.6
142 sexually abnormal double plus	143.9 ± 1.7
179 with masculine body hair	139.0 ± 1.2
125 with fibroids	142.0 ± 1.6
117 with somewhat enlarged fibroids	142.6 ± 1.5
79 with large or toxic thyroids	139.8 ± 1.8
64 with sexual anesthesia	140.5 ± 1.7
51 with partial or total hysterectomy	139.5 ± 3.3
87 with unilateral or bilateral ovariectomy	137.0 ± 2.2
188 with no pregnancies	137.8 ± 1.3
567 with children	138.4 ± 0.8
216 single between ages of 25 and 49	132.1 ± 0.8
577 married between ages of 25 and 49	131.4 ± 0.6
282 with normal menstruation, between 16 and 39	128.0 ± 0.7
283 with difficult menstruation, between 16 and 39	126.5 ± 0.6
110 over 50 with menopause past	162.2 ± 2.1
98 over 50 still menstruating	160.0 ± 2.2

that such pressures are within the range of normal for a few women. Often they seem to produce no symptoms.

A study of those between 30 and 40 with high pressures shows, again, very few who seem to be perfectly normal. One, aged 36, with a pressure of 205 systolic, was placed with the normals because the only questionable thing about her pelvic organs was some slight enlargement and hardening of the uterus. It was the sort of thing that we could not be sure about. Another with a pressure of 194 systolic, 120 diastolic, was a fine looking woman with normal appearing pelvic organs —seen during an appendectomy. The only thing against her is her celibacy. Another with pressures of 170 systolic, 105 diastolic, seems to be perfectly normal sexually. Another with 150 systolic pressure is apparently sterile and has a somewhat enlarged thyroid, an enlarged uterus and dyspareunia. She should have been put in the plus group.

Our impression from studying the rest of the women in the 30 to 39 group with high pressures is that there are quite a few who began life with normal pelvic organs, but who are already, at this age, losing some of their ovarian strength, enough so that the latent tendency to hypertension can emerge.

SUMMARY

Table 18 will enable the reader to compare quickly the means obtained in the different groups.

We have seen that the average pressure for all ages in women who seem to be sexually normal is 134.5 ± 0.7 mm. of mercury. Corrected for weight it is 133.8 ± 0.7 mm. The average in the twenties is 122.1 ± 0.7; in the thirties it is 125.8 ± 0.7; in the forties it is 135.3 ± 1.2, and after 50 it is 154.4 ± 1.7 mm.

The mean diastolic pressure for the corresponding age groups is 82 ± 0.8, 83.5 ± 0.6, 88.4 ± 0.9 and 93.8 ± 0.9.

Well proportioned women have systolic pressures that average 10 mm. higher than those of the thin, and pressures in the stout average 12 mm. higher than in the well proportioned. An allowance has to be made for these differences when any two groups of women are being studied.

The sexually abnormal have pressures that average considerably higher than do those of the sexually normal. As the sexually abnormal tend to get married a little late as compared with their normal sisters, we find that single women have pressures averaging a little higher than those of the married women.

A masculine distribution of body hair, sexual anesthesia, fibroids of the uterus, thyroid disease, and pelvic conditions requiring ovariectomy or hysterectomy are associated with high average pressures.

Abnormal menstruation, early menopause and pregnancy have no demonstrable effect.

Marked hypertension was found in a few girls who seemed to be normal sexually, but in these cases it was not of the primary type but was associated with severe forms of nephritis.

The evidence here presented supports the theory that the "essential" type of hypertension is a bodily peculiarity, inherited equally by girls and boys, but ordinarily repressed in women before the menopause by the ovarian or other related secretions. When the pelvic organs are subnormal, the disease may appear in women as early as it does in men.

We wish here to express our indebtedness to Dr. Raymond Pearl, who has so kindly come to our rescue in times of perplexity and who has gone over our manuscript. We wish also to thank Drs. R. L. McCalla, W. C. Frey and R. Franzen for help given along the way.

EXOPHTHALMIC GOITER

A FOLLOW-UP STUDY OF CASES TREATED WITH THE ROENTGEN RAY *

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Radiotherapy has been used in the treatment of hyperthyroidism for many years. The best controlled series of cases heretofore reported was that of Means and Aub [1] from the clinic of the Massachusetts General Hospital. Since then it has been increasingly popular as a means of treatment until at the present time it is being employed in many of the larger clinics throughout the country to depress the activity of thyroid glands that are producing a thyrotoxicosis. To the patient it offers a simpler, less hazardous, and more accurately controllable procedure than does surgery, with an equally good prognosis, and as a means of treatment deserves more universal usage. Only the overwhelming statistics from surgical clinics have kept it from advancing more rapidly.

The literature abounds in statistical studies of cases of exophthalmic goiter in which operations have been performed, but the results reported are either immediate results or follow-ups based on questionnaire postals or letters, which at best, with intelligent patients, is far from ideal. A personal follow-up, in which the operator or his assistant sees the patient at intervals of every six months or so for a number of years after the operation is the only way by which we can really judge the outcome of a disease. And this is not possible in large series, especially when many patients come from a distance. Hence it has seemed to me that an insight into the result of therapy and the ultimate prognosis of the disease could be gained by personal study of a small group of cases, and it is such a group of cases that are reported here.

These patients were all seen at the Presbyterian Hospital, either in the outpatient department or in the wards, and subsequently in the follow-up clinic. A secret in the success of keeping the follow-up material up to date was the fact that the patients always saw the same physician. Each felt that a personal interest was being taken in his case. This, by the way, is the secret of any successful follow-up clinic and works to the mutual benefit of physician and patient, prognosis and cure.

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1. Means, J. H., and Aub, J. C.: Basal Metabolism in Exophthalmic Goiter, Arch. Int. Med. **24**:645 (Dec.) 1919.

At the outset of these studies every lead was investigated with the hope that some group characteristics might throw certain cases together and give us some lead as to therapy. For this purpose creatin metabolism, glucose mobilization, basal metabolism and electrocardiographic studies were made in addition to careful physical examination, blood counts and the usual hospital work up. As these gave no distinct criteria, clinically similar cases varying so strikingly in these special studies, we abandoned them and came to rely on a careful clinical work up and basal metabolic studies. This great variation in apparently similar cases must become apparent to anyone who studies hyperthyroidism carefully, and must impress him with the protean characteristics of the disease. Surely hyperthyroidism as we see it in exophthalmic goiter is not a dystrophy of the thyroid gland alone. One case will manifest its chief symptoms myocardially; another outwardly of the same intensity will affect the nervous system primarily; others will pick out the gastro-intestinal tract, and some will combine any or all of these symptom complexes. It is not uncommon to have the patient come to the clinic with the exophthalmos as the chief complaint. One patient came in because of breathlessness and irregular pulse. He was fibrillating owing to a full blown exophthalmic goiter, yet his myocardial symptoms were the only things that caught the focus of his attention. Another patient came in complaining of large tonsils. She had an outstanding exophthalmos and a severe exophthalmic goiter, but none of her complaints were referable to this.

Before going into the case reports, it seems logical to take up systematically some of the features that this series of cases have revealed. Psychoses have been comparatively rare, occurring only in three cases, one of which, following a mental shock, ran a rapid down hill course terminating in a schizophrenic state and death, in spite of intensive therapy. They all were in the nature of anxiety neuroses. Restlessness that sometimes simulates a severe chorea is not uncommon. The psychosis usually clears up under therapy.

Exophthalmos is one of the most puzzling features of the disease. No satisfactory explanation of its mechanism has yet been advanced. Why it should occur in the exophthalmic goiter syndrome and not in the adenoma complex is a mystery. It is one of the earliest signs and is one of the last to disappear after recovery. In some cases it continues to a greater or less degree permanently even after recovery.

Focal infection, especially localized in the tonsils, is common. The procedure in such cases is to eliminate the focus of infection at the same time the disease is being treated. In a few of our cases the tonsils were radiated as well as the thyroid gland, with quite an amazing shrinking of the hypertrophied tonsillar tissue. One unpleasant sequela of radiating the tonsils is an acute parotitis. Apparently the roentgen

ray can cause a nonseptic inflammation of the salivary glands. This is not a serious complication, but it is quite uncomfortable and is to be avoided when possible.

As to the thyroid gland itself, there is no relation between its size and the severity of the thyrotoxicosis. The almost impalpable glands can cause the severest toxemia, while the largest sometimes show the least functional derangement. The best index here to the severity of the disease is the vascularity of the gland as manifested by large, palpable arteries, thrills and bruits. The consistency of the gland and the presence or absence of nodules is of minor importance. Substernal thyroids and persistent thymus glands are rare as judged by this series of cases, none having been discovered in any of the cases in which they were suspected and subsequent roentgenograms taken.

The heart is almost universally affected by the thyrotoxicosis. In only one or two cases of severe exophthalmic goiter was the pulse comparatively slow, from 80 to 90 to the minute. Tachycardia was a general finding. It is difficult to believe that any real organic change takes place in the myocardium, except perhaps in very toxic cases, or in long standing cases with persistent tachycardia. The majority of the patients treated with benefit show no evidence of any permanent damage to the myocardium. A not uncommon finding in the overactive thyrotoxic heart is a booming first sound with a suggestion of a presystolic rumble that resembles closely a mitral stenosis. This impurity has disappeared in the patients that have recovered clinically and metabolically. Fibrillation is not rare, having occurred in six cases of this series. Of these, three have been restored to normal rhythm, two after long standing fibrillation. Of the patients that have continued to fibrillate after recovery from hyperthyroidism, none have shown any signs of decompensation up to the present time. One was brought into the wards for quinidine therapy, but normal rhythm could not be established. Occasionally the toxemia is so severe that necrosis of the myocardium occurs. Goodpasture [2] has recently reported two cases of this condition. A high arterial pulse pressure is almost the universal finding. It is usually due to a slight increase in the systolic pressure and a greater decrease in the diastolic pressure. This is not an unusual finding in an overactive heart with a peripheral vasodilation.

In the liver focal necrosis must occur at times, though there is little evidence of this in the literature. Experimentally, it has been shown by Cramer [3] and his collaborators that thyroid fed mice at necropsy show almost a total absence of liver glycogen, whereas control animals

2. Goodpasture, E. W.: Myocardial Necrosis in Hyperthyroidism, J. A. M. A. **76**:1545 (June 4) 1921.

3. Cramer, W., and Krause, R. A.: Proc. Roy. Soc., Sec. B, **86**:50, 1913.

have the usual amount; some work by me [4] on the glucose mobilization rate in exophthalmic goiter tends to confirm this in human beings. Patients with hyperthyroidism when given glucose burned it with great readiness, but were unable to store it with anything like the usual rapidity of the normal control, and therefore had high blood sugar and a transient glycosuria. This perhaps is the reason that certain hyperthyroids develop acidosis so readily on carbohydrate restriction or on high fat diets, and might in part account for the headaches that occur, especially those early in the morning before breakfast, a not uncommon symptom in cases of severe toxemia.

The absence of free hydrochloric acid in the gastric juice has been noted in several cases. This may account for some of the diarrhea that is sometimes an annoying symptom. The administration of dilute hydrochloric acid to these patients gave symptomatic relief, and in the few on whom this has been tried it has proved beneficial. Further studies are now being pursued on this subject by the gastro-enterologic department of this hospital.

Tremor of the tongue, fingers and toes is one of the most frequent physical findings, even in mild cases. It is not unusual, however, to see tremor in other conditions simulating hyperthyroidism—especially in functional neurosis and in cases of irritable hearts in which the differential diagnosis often has to be made by basal metabolism determination. The tremor of hyperthyroidism, however, particularly that of the fingers, if observed carefully, seems to be an uncoordinated tremor; each finger will be vibrating at a different phase and they are not synchronized. The best way to elicit this tremor is for the patient to spread the fingers widely apart and for the physician to support the hand with his thumb under the carpophalangeal joint of the middle finger. Tremor of the eyelids, arms, legs or whole body may occur, and the degree of tremor is not always commensurate with the toxicity. The body tremor can at times be choreiform. One case was so severe that it simulated Huntington's chorea.

Muscular weakness and fatigability usually are early signs. This for the most part is general, but not uncommonly affects one group of muscles more than another. One rather common group affected is the extensors of the thigh. The weakness of these muscles may be so extreme that the patient will volunteer the information that it is impossible to get up even very low steps, though he will be able to walk with ease on a level ground.

In well marked cases, evidence of vasomotor irritability is almost the rule. Flushing, dermatographia and sweating are evidences of a

4. Sanger, B. J., and Hun, E. G.: Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:297 (Sept.) 1922.

sympathetic stimulation, and can be accentuated, as can any other type of sympathetic irritability, by the subcutaneous injection of epinephrine. The Goetsch test, based on this response to epinephrine, has largely fallen into disuse as we see the same response in nonthyrotoxic cases of sympathetic irritability as in thyrotoxic cases.

A great deal of stress has been put on the value of the differential blood picture as a diagnostic aid. It was said that there was almost always present a distinct lymphocytosis. It was somewhat surprising, therefore, to discover that in the majority of these cases the differential picture was essentially normal. The total number of red blood cells, white blood cells and the hemoglobin content usually are normal in uncomplicated cases.

In the female the evidence of relation of the ovarian system to the disease is striking. It is not uncommon to have some type of menstrual disturbance associated with hyperthyroidism, most usually an irregularity of the menses or an amenorrhea. The common observation of the increase in size of the thyroid at puberty, during the menstrual period, or during some phase of pregnancy is another evidence. Pregnancy occurring in the course of treatment or in recently cured cases will frequently rekindle a thyrotoxicosis. In three of our cases this has occurred, but the recurrence was promptly relieved by further treatment.

In all cases of true exophthalmic goiter the basal metabolism is elevated above normal. Almost every symptom can be referred to the increased cellular metabolism. The thyroid hormone is a cell stimulant, hence the increase of total metabolism in all cases of hyperthyroidism. The basal metabolism therefore gives us the best index of the toxicity of the gland. The apparent derangement of carbohydrate metabolism is one of storage, not of utilization; that is, there is no fault with specific carbohydrate utilization. It is probably because of this failure to store carbohydrate that the fasting quotient in cases of exophthalmic goiter is somewhat lower than normal, being somewhere around 0.76.

A detailed case history of all patients included in this paper will not be given, as they all presented typical histories and physical findings of exophthalmic goiter. Only those, therefore, that for one reason or another seem of importance or point out some particular phase of the problem will be cited in brief.

Three cases with auricular fibrillation seem especially interesting. They do not include the whole number of cases with this complication, but in their essential features they epitomize the group.

REPORT OF CASES

CASE 1.—E. R., a white traveling salesman, aged 35, married, entered the hospital, Feb. 17, 1920, complaining of cardiac palpitation, nervousness and shortness of breath. The family history was negative, except for the fact that one

sister was supposed to have had goiter. The previous history was essentially negative. The present illness dated back three years, when the patient had first noticed rapid heart action. He later developed tremor of the hands, excessive sweating, and dyspnea on exertion. Struma had been present for about one year. Some loss of weight had occurred early in the disease, but at the time of admission the patient had regained his normal weight. Tonsillitis also had occurred early in the disease, and the patient had had his tonsils removed. The shortness of breath recently had increased to such an extent that he sought hospital attention. Physical examination showed a well developed and well nourished young man weighing 63.6 Kg. The skin was moist and flushed. The patient appeared somewhat nervous, but was without frank exophthalmos, though the eyes were bright and somewhat staring. Joffroy and Moebius signs were present. The thyroid gland was diffusely enlarged, but no bruit or thrill could be made out. The heart was normal in size and position; its action was irregular in force and rhythm. The character of the heart sounds were suggestive of mitral stenosis, but no murmurs were definitely heard. There was a fine tremor of the fingers and toes. The blood pressure was 150 systolic, 80 diastolic. Physical examination was otherwise negative. The electrocardiogram showed auricular fibrillation; there was a marked pulse deficit. The basal metabolism on admission was 55 per cent above normal. The sugar tolerance test (100 Gm. of glucose by mouth) gave an essentially normal response.

Under rest in bed and digitalis therapy the pulse deficit cleared up, although the heart action was still irregular in force and rhythm. October 23, the basal metabolism was 46 per cent above normal, with a respiratory quotient of 0.72.

The patient was discharged, March 6, much improved symptomatically, but with his heart still fibrillating and his basal metabolism still high. After leaving the hospital ambulatory treatment consisted in roentgen-ray therapy. June 23, after six treatments, the basal metabolism was still 51 per cent above normal, the pulse was 88, but still irregular, and digitalis was continued. August 16, after the eighth treatment, quite striking changes were manifest. He had felt a steady improvement, and finally there had been a disappearance of all his symptoms: shortness of breath, tremor, nervousness. He had been gaining in weight. On physical examination he now appeared calm; there was only a slight tremor, the struma persisted, although it was somewhat smaller, and the heart rate was regular and 84 to the minute. The basal metabolism had decreased to 8 per cent below normal. The electrocardiogram showed normal rhythm. Roentgen ray and digitalis were now discontinued and, September 25, the patient returned in excellent condition, with a metabolic rate of 6 per cent above normal. He is now back on the road as a traveling salesman, and doing his work without any difficulty. The heart action has remained entirely normal, and he has no signs and symptoms referable to his former disease.

CASE 2.—D. S., a housewife, aged 26, entered the hospital for the first time, May 14, 1917, complaining of tremor of the fingers and excitability.

The family and personal histories were essentially negative. She dated the onset of the present illness from the birth of a child, Nov. 15, 1917. In December of that year she had an abscess of the breast, and soon after this she observed the tremor of her fingers and the increased irritability. Nine months later she discovered that her neck was getting larger and that she tired more easily. Three months before admission she began to have headaches, insomnia and sweating. She was conscious that she always felt warm and that she was losing weight. The weight on admission was 45.5 Kg.

Physical examination revealed a moist, warm skin, prominent eyes, with a distinct lid lag, large, infected tonsils, and marked tremor of the fingers. The thyroid was diffusely enlarged, the right lobe being somewhat larger than the left, elastic in consistency, with a systolic bruit and thrill over the gland. The heart was slightly enlarged, with a presystolic and systolic murmur at the apex and to the left side of the sternum. Otherwise the physical examination was essentially negative.

Under rest and high caloric diet she improved slowly, and was discharged, September 30, having gained 7.7 Kg. She was treated for a while by psychotherapy with good results, till June, 1919, when she was lost sight of. She came back to the hospital, March 30, 1921, with a history of fever and weakness of three weeks' duration, and generalized pain. Except for emaciation and fever, the physical examination was much the same as on the previous admission. The weight on admission was 40.9 Kg. It was decided that she had acute rheumatic fever, and she improved on salicylates. Her basal metabolism at this time was about 40 per cent above normal. During her stay she developed auricular fibrillation. Quinidine was given without any results.

May 16, radiotherapy was started and she received twenty-seven treatments between that time and June, 1923, with progressive improvement. She continued to fibrillate until some time after February, 1922. When seen in April of that year the pulse was regular and an electrocardiogram showed normal rhythm. She is now back to her normal status after a long, rather stormy course, entirely well, with a normal basal metabolism.

CASE 3.—B. S., a single white man, aged 34, a pressman, entered the hospital, May 8, 1922, complaining of nervousness and exophthalmos. The family history was negative, and the past history was negative except for the fact that he had had typhoid at 15.

The present illness dated back to the spring two years before, when the patient began to suffer from insomnia and a tremor of the hands that interfered with his work. Finally he had to give up and go to the country because of what was termed a "nervous breakdown." He lost 9 Kg. and had profuse sweating and palpitation on the least exertion. In the fall he was able to go back to work much improved. Six months before admission friends had first noticed the prominence of his eyes, and he came into the hospital especially because of this. The chief findings were a moist, warm, flushed skin, extreme exophthalmos with all related eye signs, and gingivitis. There was marked carotid pulsation. The thyroid gland was not enlarged. He had a rapid, irregular pulse, and an electrocardiogram showed auricular fibrillation. The basal metabolism on admission was 55 per cent above normal.

On rest in bed, high caloric diet and two radiotherapy treatments this came down to 34 per cent above normal and the patient was discharged improved, to continue on ambulatory treatment. He had in all fourteen treatments. He had a subsequent admission to the hospital for quinidine therapy, but his fibrillation persisted. He now has no evidence of any myocardial insufficiency in spite of this, and is back on his job as a pressman, working from eight to twelve hours a day. He has had a normal basal metabolism, and has been free of all symptoms of hyperthyroidism since April, 1923.

In one case that occurred early in our series a hypothyroid state was produced, which has persisted in spite of thyroid medication. The following shows distinctly that the cumulative effect of radiation must be kept in mind:

CASE 4.—F. M., a single white man, aged 40, a mail clerk, came into the dispensary, July 16, 1921, complaining of goiter. The family and personal histories were negative except for the fact that the patient had had influenza in 1919. He dated the onset of the present illness from the attack of influenza, when he had noticed that his neck was getting larger. In the spring of 1920 he was at home for ten weeks because of nervousness, palpitation and shortness of breath. He was better after rest, and was able to go back to work. He came to the dispensary chiefly for nervousness and the goiter.

On physical examination he appeared nervous and excitable. There was a slight exophthalmos, with slightly positive eye signs. There was diffuse enlargement of the thyroid, the right lobe being somewhat larger than the left. A thrill

and bruit were present over both lobes. The heart was not enlarged. S_1 was loud and booming at the apex, followed by a low pitched systolic murmur. There was a presystolic gallop at the base. The reflexes were increased. The basal metabolism done July 16, 1921, was 38 per cent above normal, with a pulse of 100.

He had five radiotherapy treatments and, October 6, the basal metabolism was 2 per cent below normal, with a pulse of 68. All signs and symptoms of the thyrotoxicosis were gone except some shortness of breath on exertion. June 19, 1922, the basal metabolism went up to 15 per cent above normal, and two more treatments were given. The basal metabolism then went down to 25 per cent below normal, and it has remained approximately the same ever since.

He is back at work as a railroad mail clerk, but in spite of 4 grain (0.26 Gm.) doses a day of thyroid extract, his basal metabolism remains below normal.

Three patients were so toxic that they were not considered good surgical risks. They responded quite strikingly to roentgen-ray treatment, as their histories will demonstrate:

CASE 5.—G. R., a woman, aged 28, a machine operator, entered the hospital, June 19, 1924, complaining of swelling of the neck of ten months' duration.

The family history was entirely negative, and the past history was negative except for the fact that she had had nose and throat infections for the last five years. She had had a tonsillectomy in 1919.

The onset of the present trouble dated back four years, when she first noticed nervousness, palpitation and loss of weight. She first noticed the swelling of the neck ten months before admission. Her own physician gave her roentgen-ray treatments (?) for a short while, with some benefit. Recently she was more nervous, and had a sinus infection.

On physical examination she was apprehensive and overactive. There was distinct exophthalmos. The thyroid was enlarged and rubbery in consistency, and bruit was present. The pulse rate was 110. There was marked tremor of the fingers. The admission basal metabolism was 60 per cent above normal. She was given rest and treated with sedatives without results; she was extremely restless and stimulated.

She improved on Lugol's solution and her basal metabolism came down, but at once rose again when Lugol's solution was omitted. This procedure was repeated with the same results. She was then started on radiotherapy, and straightway began to improve. After five treatments she had lost all her symptoms. She has been back at her rather strenuous work for almost a year now, without any discomfort referable to her previous hyperthyroidism.

CASE 6.—A. W., a man, aged 48, a newsdealer, entered the hospital, June 25, 1923, complaining of weakness, nervousness, swelling of the neck and loss of weight, extending over the previous three years. The family history was negative except for a strain of epilepsy, and the patient's own history was entirely negative. Three years before admission, following a shock, he began to have tremor of the hands and nervousness, and noticed that he tired easily. Soon after this his neck began to swell, and though his appetite was increased, as was his food intake, he lost weight. Recently he had palpitation with a definite increase of all his symptoms.

The physical examination revealed an apprehensive, anxious man, with moist, warm skin. There were patches of leukoderma over the face, hands and crural regions. There was a suggestive exophthalmos, with no lid lag, but a widening of the palpebral fissure. The tonsils were moderately hypertrophied. The thyroid was diffusedly enlarged. The heart was enlarged and the pulse rapid; there was a fine tremor of the fingers. A basal metabolism done June 28, was 79 per cent above normal. Under rest and a high caloric diet he developed a severe diarrhea with further loss of weight. He was started on radiotherapy, and received three treatments before he left the hospital. He had a distinct anxiety neurosis during

his stay at the hospital, and finally left against advice, not much improved. Subsequent to his discharge he had two more treatments. The basal metabolism promptly fell to normal, where it has remained ever since. He has led an active life for the last two years, has been entirely relieved of all previous symptoms, and has gained 20 Kg. since the time he was first seen.

CASE 7.—M. K., a housewife, aged 29, married, entered the hospital, May 9, 1923, complaining of goiter. Her father had died of heart trouble, and one aunt had a large goiter. The patient's own history was negative except for a pelvic operation seven months before admission. She had first noticed swelling of the neck while in Ireland two years before admission. Following the operation seven months before admission, she began to have hot flushes and nervousness. She soon developed nausea and vomiting, with resulting weakness and loss of weight. Subsequently nervousness became worse, and she noticed palpitations and shortness of breath. On physical examination she was seen to be a restless, agitated young woman, with moderate exophthalmos and positive eye signs. The thyroid gland was diffusely enlarged, soft, with evidence of increased vascularity. The heart was slightly enlarged and overactive; there was a soft systolic murmur at the apex; the rate was 105 and regular. There was a fine tremor of fingers, moist hands and hyperactive reflexes. The basal metabolism, May 22, 1923, was 102 per cent above normal. She had a distinct anxiety neurosis with a great deal of motor overactivity. With rest in bed, sedatives, and radiotherapy she began to improve but left the hospital against advice. She then was treated in the follow-up clinic and responded most satisfactorily to radiotherapy. In all she had sixteen treatments.

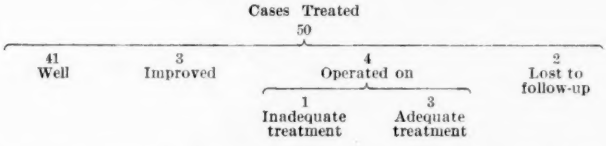
We now come logically to the treatment of these cases. It seems foolish to talk about remissions of the disease, or to say that it is self limited and let the matter of therapy rest there. Nor can we believe that masterful neglect will cure cases of exophthalmic goiter. Many of the cases in this series give long histories of thyrotoxicosis, with rest and all other types of therapy interspersed in their course. In spite of this most of them showed a progressive downward trend. It seems only reasonable in a disease that has such marked constitutional effects to treat it actively and reduce the general toxemia and increased metabolism as soon and as simply as possible, before any permanent organic change has occurred. It is not uncommon to see patients after treatment cured of their hyperthyroidism but having a residual myocarditis, or some other related organic change, which either partially or totally disqualifies them for an active, normal existence. One patient in this series was practically relieved of all signs and symptoms of exophthalmic goiter, but died because her myocardium was too badly damaged to develop any compensation.

Radiotherapy offers a simple form of treatment. It rarely causes the patient any discomfort at all. Only occasionally has there been any unpleasant reaction, characterized by malaise, nausea and vomiting, lasting at most from twenty-four to forty-eight hours. A great many of the cases in this series were treated as ambulatory patients, and went about their usual occupations, with advice to rest as much as possible and to take a high caloric diet. Only the patients that had severe myo-

cardial symptoms were advised to take a complete rest. From the case reports there can be little doubt of the efficacy of this form of therapy. One case that occurred early in our series proved conclusively that radiotherapy has a distinctly depressing action on the thyrotoxic gland. The history has already been cited in this paper as an example of the cumulative action of the roentgen ray (case 4). This is the only case in which treatment has produced a subthyroid state. Since this case has occurred we do not treat a secondary rise in the basal metabolism so promptly, as we feel that there is a distinct cumulative effect from the radiation, lasting sometimes several months.

The treatment has varied a little, with the several roentgenologists who have directed the radiotherapy, as to dosage and frequency of treatment, but when reduced to equivalents was essentially the same. The dosage used at present is 90 K. V.; 16 inch target skin distance; 5 milliamperes for twelve minutes; 3 mm. aluminum filter.

Up to the present time we have treated fifty patients with radiotherapy. The results may be epitomized as follows:



There have been secondary rises in basal metabolism and concomitant reappearance of symptoms in four cases. All these have responded promptly to further radiotherapy, and have needed generally but one or two additional treatments.

The average number of treatments necessary for results has been ten. The greatest number of treatments given any one patient, with final recovery, was twenty-seven. The smallest number needed for the same end was three. There is no way of predicting beforehand how stubborn the cases are going to be to treatment. Not infrequently those with only a moderate rise in the basal metabolism are the most refractory.

The improvement in symptoms following radiotherapy usually is quite rapid. In most cases after three treatments, the patients feel distinctly better and appear less toxic. One of the most striking things noted is the early tendency to gain weight, and this often before there has been any fall at all in the basal metabolism. The extreme nervousness and sleeplessness soon disappear in the cases that are responding to treatment. In early cases palpitation and tachycardia are soon lost, but this symptom complex is more persistent in the cases of longer standing, as might naturally be expected. When there has been a real myocardial change this may persist for a long time after all symptoms

of the disease have disappeared, and the basal metabolism has reached normal. In ocasional cases in which the damage has been great, it may continue permanently. Exophthalmos usually is one of the last things to disappear, though in occasional cases it has disappeared like magic after only a few treatments. Usually it persists in some degree for a long time after the basal metabolism has reached normal, and in cases in which it has been extreme may never recede much, although all the other symptoms will have gone and the patient be entirely over his hyperthyroidism. Tremor also tends to remain till the metabolism has struck a normal level, when it almost universally disappears.

The value of careful basal metabolism determination in the follow-up of these cases cannot be overestimated. It is the gage by which we regulate our treatment and reduce the activity of the gland to normal with the least possible chance of doing too little or too much. Our system has been to give a series of three treatments three weeks apart, followed by a basal metabolism three weeks after the last treatment, and subsequent series of treatments as indicated by the results of the test. Treatments must be given regularly every three weeks, till the basal metabolism is brought within the normal limits. Any irregularity militates against the best results. When the metabolism has reached normal, we follow the patient with basal metabolism determinations at monthly or two monthly intervals for the first four to six months, after that every six months from then on, but the patients are instructed to come in at any time between appointments if a return of their previous symptoms is noted. In this way any recurrence of a thyrotoxicosis is made out early, and can be depressed promptly by little additional radiotherapy. A long continued follow-up with frequent basal metabolism determinations is the only sound way of knowing the outcome of treated cases, and for this a personal follow-up is absolutely essential.

The important point in the clinical course of the cases included in this series is given in the accompanying tables. Some of the most recent cases have not had a very long follow-up, but are being included in this series, as an attempt to follow the histories for a number of years will be zealously made with a view toward increasing our knowledge of the ultimate results of therapy and the final prognosis of the roentgen ray as a therapeutic agent. It will be seen that radiotherapy does not cure all cases, just as operation does not; but in a final analysis the results are as good with much less inconvenience and economic disability to the patient. In a longer followed series it is my impression that the results will be better, as here we have an agent whose dosage and use can be closely controlled. It is not a haphazard matter of taking out just enough gland, not too much nor too little, a thing that comes only after a great deal of surgical experience, and even then does not lend itself to great accuracy. With radiotherapy controlled by frequent

Summary of Cases

Case	Date First Seen	Duration of Symptoms	Initial: Weight, Kg.	Initial: Basal Metabolism, per Cent	Initial: Pulse	Treatment	Date Last Seen	Last: Weight, Kg.	Last: Basal Metabolism, per Cent	Last: Pulse	Became Symptom Free with Normal Basal Metabolism	Duration of Follow-Up	Remarks
1	1/28/20	1 yr.	54.9	+31	104	3 roentgen-ray; secondary rise; 3 roentgen-ray	5/ 8/25	61.7	— 2	68	10/14/21	5 yr. 8 mo.	Previous thyroidectomy; entirely well after radiotherapy; following pregnancy had slight secondary rise
2	2/ 7/20	3 yr.	63.7	+55	106 (fibrillating)	8 roentgen-ray	3/12/25	75.2	+ 6	84	8/16/20	5 yr. 7 mo.	Fibrillation; normal rhythm established when basal metabolism became normal
3	3/30/20	6 mo.	59.7	+46	100	6 roentgen-ray	1/ 4/21	63.8	+37	...	.....	10 mo.	Postoperative case; irregular treatment; slight improvement
4	4/ 6/20	1½ yr.	50.2	+28	92	16 roentgen-ray	11/ 7/21	62.8	+21	86	.....	1 yr. 7 mo.	Slight improvement; moved away while still under treatment; subsequently operated on
5	6/12/20	3 yr.	56.3	+47	116	13 roentgen-ray	11/30/21	59.5	+23	100	.....	1 yr. 6 mo.	Improved; lost to follow-up while still under treatment
6	6/18/20	2 yr.	47.2	+55	104	8 roentgen-ray	9/19/23	57.7	—11	64	10/ 2/22	5 yr. 3 mo.	Entirely well
7	8/18/20	8 mo	51.6	+35	84	18 roentfien-ray	7/22/25	56.4	+32	100	10/16/22	5 yr. 1 mo.	Improved somewhat; subsequently operated on
8	11/ 9/20	1½ yr.	50.6	+56	120	13 roentgen-ray	5/12/24	59.0	+13	92	2/28/23	4 yr. 10 mo.	Entirely well; slight secondary rise; exophthalmos persists
9	12/ 3/20	7 yr.	48.8	+43	104	14 roentgen-ray	4/24/25	57.9	+ 2	84	10/24/22	4 yr. 9 mo.	Entirely well
10	12/21/20	2 mo.	55.2	+63	108	9 roentgen-ray	10/31/21	60.5	+60	112	.....	8 mo.	Would not take treatments regularly; very slight improvement; operation elsewhere; died
11	12/31/20	8 mo.	39.0	+65	120	14 roentgen-ray	7/25/21	36.5	+47	120	.....	6 mo.	Lost to follow-up clinic before treatment was completed; improved
12	3/ 1/21	8 mo.	57.7	+26	96	15 roentgen-ray	3/14/25	55.0	± 0	80	4/27/22	4 yr. 6 mo.	Entirely well; lost to follow-up clinic 2 years after recovery
13	3/14/21	Indef.	59.5	+37	82	13 roentgen-ray	6/24/25	55.2	+ 2	76	4/ 4/24	4 yr. 6 mo.	Entirely well
14	4/ 1/21	2½ yr.	49.0	+58	116 (Irregular)	10 roentgen-ray	10/10/24	57.2	— 5	68	2/18/22	4 yr. 5 mo.	Improved only slightly; subsequently operated on; now entirely well
15	4/ 8/21	8 mo	55.4	+99	144	24 roentgen-ray	9/19/25	72.0	+10	68	9/26/24	4 yr. 5 mo.	Entirely well
16	4/ 9/21	4 yr.	47.2	+35	100	24 roentgen-ray	9/18/25	51.5	— 8	64	1/31/23	4 yr. 5 mo.	Entirely well

17	4/16/21	3 wk.	49.0	+40	96	14 roentgen-ray	12/20/21	46.0	+37	104	.....	8 mo.	Well for 7 months; then developed carcinoma of stomach with rise in metabolism; died
18	4/23/21	Indef.	53.2	+73	132	11 roentgen-ray	2/ 9/25	64.7	+ 6	84	6/ 1/22	4 yr. 5 mo.	Entirely well
19	5/ 4/21	5½ yr.	39.3	+40	112 (Irregular)	27 roentgen-ray	2/18/25	52.9	± 0	72	7/19/23	4 yr. 4 mo.	Fibrillation; returned to normal after treatment; entirely well
20	7/16/21	2 yr.	54.5	+38	100	7 roentgen-ray	2/19/25	66.0	—13	56	3/ 3/22	4 yr. 2 mo.	Now has hypothyroidism; taking thyroid extract
21	9/ 6/21	3 yr.	59.0	+105	102	11 roentgen-ray	3/21/25	63.0	+15	80	11/13/23	4 yr.	Entirely well
22	9/10/21	4 mo.	52.0	+38	88	13 roentgen-ray	4/23/25	54.5	+ 9	80	9/10/23	4 yr.	Entirely well
23	9/12/21	7 mo.	49.6	+48	138	14 roentgen-ray	9/21/25	53.2	+ 6	84	6/29/25	4 yr.	After first basal metabolism lost for 2 years; then treated; well
24	10/10/21	3 yr.	54.2	+42	120	20 roentgen-ray	6/ 5/25	51.0	± 0	76	5/25/23	3 yr. 11 mo.	Entirely well
25	10/20/21	8 yr.	60.8	+30	100	14 roentgen-ray	9/26/25	54.8	+ 4	72	6/29/22	3 yr. 11 mo.	Entirely well
26	2/ 7/22	8 mo.	50.0	+82	144	12 roentgen-ray	9/21/25	71.2	+12	92	4/20/25	3 yr. 7 mo.	Had hypertension, also had secondary rise; now normal; hypertension persists
27	3/ 3/22	4 yr.	76.4	+23	100	7 roentgen-ray	9/16/25	70.5	+18	100	9/ 6/22	3 yr. 6 mo.	Entirely well
28	3/14/22	7 mo.	61.5	+50	128	11 roentgen-ray	9/19/25	66.8	— 2	80	5/11/23	3 yr. 6 mo.	Entirely well
29	5/20/22	6 mo.	56.2	+55	92	14 roentgen-ray (irregular)	6/15/25	72.1	—18	76 (irregular)	4/19/23	3 yr. 4 mo.	Entirely well; exophthalmos persists; still fibrillating
30	5/25/22	5 yr.	48.4	+63	112	13 roentgen-ray	9/17/25	57.0	+ 8	72	7/11/24	3 yr. 4 mo.	Entirely well
31	6/ 9/22	1 yr.	56.5	+23	116	6 roentgen-ray	9/23/25	65.0	— 3	80	8/30/23	3 yr. 3 mo.	Entirely well; has some exophthalmos
32	8/24/22	2 yr.	50.7	+52	120	8 roentgen-ray	4/24/25	60.0	— 7	84	3/ 6/23	3 yr. 1 mo.	Entirely well
33	9/16/22	Indef.	62.0	+35	106 (Irregular)	10 roentgen-ray	6/30/25	68.0	+ 2	64 (irregular)	8/23/23	3 yr.	Entirely well; still fibrillating; has large fibroid
34	9/22/22	4 yr.	38.6	+48	100	3 roentgen-ray	3/ 1/23	38.5	+24	100	.....	.....	Was entirely well when last seen
35	10/10/22	1 yr.	45.6	+62	100 (Irregular)	6 roentgen-ray	2/ 3/23	45.5	+35	104 (irregular)	.....	4 mo.	Improved greatly under treatment; died of severe myocarditis and decompensation
36	10/14/22	4 wk.	50.0	+41	120	15 roentgen-ray	9/18/25	51.0	+11	76	5/20/24	2 yr. 11 mo.	Entirely well
37	1/16/23	4½ yr.	61.2	+68	132	7 roentgen-ray	4/ 3/25	64.6	+ 4	84	8/16/23	2 yr. 8 mo.	Entirely well
38	5/22/23	6 mo.	41.1	+102	120	16 roentgen-ray	3/24/25	62.1	+ 4	68	10/11/24	2 yr. 4 mo.	Entirely well
39	6/11/23	6 mo.	45.3	+44	100	6 roentgen-ray	7/ 7/25	50.3	— 8	68	11/15/23	2 yr. 3 mo.	Entirely well
40	6/19/23	1 yr.	40.8	+68	132	10 roentgen-ray	10/ 2/25	45.0	—10	72	2/19/24	2 yr. 3 mo.	Entirely well
41	6/21/23	4 mo.	45.5	+37	116	3 roentgen-ray	3/10/25	52.8	± 0	60	8/23/23	2 yr. 3 mo.	Entirely well
42	6/28/23	3 yr.	56.8	+79	108	5 roentgen-ray	9/22/25	75.6	— 3	76	11/ 9/23	2 yr. 3 mo.	Entirely well
43	7/16/23	17 yr.	65.3	+30	100	3 roentgen-ray	3/12/24	68.7	+ 9	84	9/13/23	2 yr. 2 mo.	Entirely well
44	8/ 6/23	2 mo.	52.8	+52	128	14 roentgen-ray	8/15/25	59.0	+19	124	5/16/25	2 yr. 1 mo.	Greatly improved; still has myocardial symptoms
45	8/20/23	Indef.	47.2	+49	112	11 roentgen-ray	1/10/25	66.4	— 2	68	5/14/24	2 yr. 1 mo.	Entirely well
46	10/31/23	6 mo.	60.2	+43	112	7 roentgen-ray	9/12/25	68.1	+10	96	6/16/25	1 yr. 11 mo.	Well
47	11/23/23	4 mo.	57.7	+38	92	5 roentgen-ray	4/ 2/25	68.3	± 0	72	4/30/24	1 yr. 10 mo.	Well
48	12/13/24	2 wk.	61.2	+34	114	6 roentgen-ray	5/ 1/25	65.7	+ 4	88	6/23/24	1 yr. 9 mo.	Well
49	2/19/24	10 mo.	57.5	+60	120	5 roentgen-ray	4/25/25	57.5	+ 4	64	10/ 9/24	1 yr. 8 mo.	Entirely well
50	6/18/24	2 yr.	51.4	+59	96 (Irregular)	4 roentgen-ray	12/16/24	54.9	+12	76	11/18/24	1 yr. 3 mo.	Well

basal metabolism determinations, we can depress the activity of the gland to within normal limits and by a watchful follow-up detect the first tendency to a secondary rise, and if this should occur, promptly institute further treatment.

SUMMARY

Fifty patients with exophthalmic goiter have been carefully studied under roentgen-ray therapy. They were followed at frequent intervals during their course of treatment and subsequent to their recovery, with basal metabolism and clinical observations. Some have been followed for as long as five years. The great majority, 82 per cent, became entirely well and remained so. Of the remaining 18 per cent, 6 per cent were improved, 8 per cent were operated on, and 4 per cent were lost to the follow-up clinic during the last year, so that the ultimate result is doubtful.

On the whole, the roentgen ray offers a safe and satisfactory therapeutic procedure, with a high percentage of cures, in cases of exophthalmic goiter.

AN OCCUPATIONAL DISEASE AMONG ZINC WORKERS *

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CINCINNATI

Any toxic properties of zinc resulting in chronic industrial disease are commonly denied. Recognition is given to an acute form of zinc poisoning under such designations as "spelter chills," "zinc fever," "brass founders' ague," "smelter shakes," etc. As early as 1888, Simon [1] in his description of this acute zinc poisoning records the absence of any chronic manifestations. Hayhurst [2] states, "The physician must get away from the idea of attempting to diagnose chronic zinc or brass poisoning, as there probably is no such condition." Later this statement is mitigated in discussing the possible chronic effects of brass poisoning [2]: "In Chicago the fact that 85 per cent of 1,761 foundry workers (brass) were under 40 years of age, and only 1 per cent over 50 years, was explained by employers as due to 'slowing up' or beginning decrepitude, and by workmen, as gradual incapacitation from the inhalation of brass fumes and the strain of work. The constant intake and elimination of unusual amounts of zinc and copper from the system, along with the repetition of brass chills or the constantly forced immunity to the same, are enough to cause degenerative diseases. . . ." Seiffert [3] advocates the recognition of a chronic poisoning among zinc smelters from zinc carbonate and zinc sulphate. The principal evidences of this condition are exhibited in gastro-intestinal lesions. Hayhurst,[2] in commenting on this work, fails to agree that this constitutes chronic zinc poisoning: "It would seem rather to be a local irritative reaction due to the zinc salts mentioned."

It is generally conceded that workers in zinc processes often present chronic industrial diseases. These conditions are usually blamed on antimony, arsenic or lead, which are found in these processes as impurities either in the zinc or in the substances used in conjunction with zinc,

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1. Simon, R. M.: Remarks on Brassworkers' Diseases, Brit. M. J. **1**:887, 1888.

2. Kober and Hayhurst: Industrial Health, Philadelphia, P. Blakiston's Son & Co., 1924, pp. 333, 342, 329, 330.

3. Seiffert: Beteiligung von Blei und Zink am Zinkhuttensiechtum mit Bermerkungen über hygienische Massnahmen in den Zinkhutten, Oeffentliche Gesundheitsplege, 1918, **3**:44.

such as sulphuric acid. The characteristics of these occupational diseases (lead, arsenic and antimony) are fairly well known. However, on close examination of workers in zinc (galvanizers) the manifestations of their diseases do not always convincingly coincide with these known characteristics.

Tradition has injected many trite statements into the literature of zinc toxicology, such as, "metallic zinc is per se nontoxic"; "only caustic salts of zinc are harmful"; "zinc is not stored in body tissues." Slowly these traditions are being broken down. Mallory and Parker [4] have produced a nephritis in animals as the result of subcutaneous implantation of pure metallic zinc. Several workers [5] have detected stored zinc in the liver, muscles and (or) other tissues, both in man and in the lower animals. The gastro-intestinal irritation, long attributed to the local action of swallowed zinc salts, has been demonstrated following their intravenous injection.[6]

It is the purpose of this article to assemble the available evidences supporting the occurrence of chronic zinc poisoning, and to correlate these evidences with the tentative findings from our own work in two zinc industries.

ACUTE ZINC POISONING: "SPELTER CHILLS"

Although acute zinc poisoning is a well established disease entity, no satisfactory explanation exists as to the mechanism through which it is induced. Hayhurst [2] believes that a reaction akin to anaphylaxis is caused by the zinc fumes searing the mucous membranes of the upper respiratory tract. Since zinc may be found in the urine and feces following an attack, others believe that the condition represents a direct systemic action of the zinc. Whatever the explanation may be, it is believed that zinc oxide alone is capable of producing zinc chills. In 1845 Blandet [7] supplied an accurate description of this disease condition in connection with the founding of brass.

The physiochemical state of zinc oxide in the form of vapors recently derived from molten zinc is definitely unlike that of the zinc oxide powder used in paints, linoleum, rubber, etc. The toxicity of the latter form is regarded as of minor significance as compared with the quick and severe manifestations at times following the inhalation

4. Mallory, F. B., and Parker, Frederick, Jr.: Experimental Intracapillary Glomerulonephritis, Proc. Am. A. Path. & Bacteriol., 1925.

5. Ghigliotto, C.: The Normal Existence of Zinc in the Human Organism, Chem. Abstr. **14**:1373 (May 10) 1920. Rost, E.: Zinc and Copper, Regular Constituents of the Human Body, Die Umschau, 1920, **24**:201-202.

6. Schwartze, E. W., and Alsberg, C. L.: Pharmacology of Cadmium and Zinc with Particular Reference to Emesis, J. Pharmacol. & Exper. Therap. **21**:1 (Feb.) 1923.

7. Blandet: Colique de cuirre, Ann. d'hyg. **33**:461, 1845.

of zinc fumes present around galvanizing, zinc smelting, brass founding, etc.

The basis of this difference in physiologic effects is discussed in detail by Drinker.[8] Reference is made to Drinker's excellent article for a critical review of the literature of zinc oxide toxicology.

Impurities (lead, arsenic, cadmium, antimony) need scarcely be considered as possible factors in the causation of zinc chills since the work in 1910 of Lehmann.[9] He was able to produce typical zinc chills from the burning of chemically pure zinc.

Opportunities for acute zinc poisoning are much greater in founding alloys of zinc wherein the metals with which the zinc is alloyed have a higher melting point, as in the manufacture of brass. The zinc constituent has a melting point of 419.4 C., while copper melts at 1,083 C. In a mixture of copper, 75 per cent, and zinc, 25 per cent, the melting point of the mass is about 920 C., which is the approximate boiling point of zinc. Although a vapor tension of zinc exists at a much lower temperature than its boiling point, this higher temperature favors the production of a state of zinc oxide capable of inducing acute zinc poisoning.

In galvanizing, acute zinc poisoning is rare under normal operating conditions although zinc fumes arise in abundance. This is owing to the low temperature generating these zinc fumes, this being only about 468 C. When, however, galvanzing pots are in need of repair, and the fire is drawn, it is sometimes necessary to take out the remnants of zinc through melting with oxyacetylene torches. This higher temperature favors the ready occurrence of zinc chills.

After exposure for a few hours to recently burned zinc oxide, the mucous membranes, eyes and bronchi have a feeling of dryness and of soreness. This may lead to a "hacking cough," to a feeling of a "belt being around the chest." The workers become weak, may vomit or be nauseated; headaches are frequent. The foregoing may take place at the foundry but more often is first noticed after leaving the work place. The victim becomes chilly and goes through the usual characteristics of a malaria-like chill. Nothing greatly aids in obtaining warmth. This period of distinct chills may last for the short period of thirty minutes or may continue throughout the greater portion of the night (occasionally it occurs during the day time). During this stage and for some hours thereafter, there is an intense thirst not easily satisfied. Hot drinks are acceptable; hot milk is often used. Both objectively and subjectively the patient is severely ill. At times the condition disappears by crisis asso-

8. Drinker, P.: Certain Aspects of the Problem of Zinc Toxicity, J. Indust. Hyg. **4**:177-197 (Aug.) 1922.

9. Lehmann: Arch. f. Hyg. **72**:358-381, 1910.

ciated with profuse perspiration and deep sleep. On awaking some patients are entirely recovered except for weakness and distaste for food. Others describe a continuous lassitude over a period of days, usually calling for catharsis.

New workers, and old workers who have been away, are more apt to be afflicted. Wet weather favors the occurrence of zinc chills. Hayhurst [2] states that about 75 per cent of workmen regularly employed develop an apparent tolerance.

There is no reason to believe that if there is a chronic form of zinc poisoning that this acute form is a forerunner or is necessarily related. In our cases of possible chronic zinc poisoning only one of the patients has given a history of antecedent zinc chills.

GENERAL TOXICOLOGY OF ZINC

Zinc may be found in various human tissues and excreta as a result of eating foods containing zinc. Shell-fish are known normally to contain zinc.[10] Van Itallie,[11] in discussing the normal content of zinc, arsenic and copper in the human body, reports the finding of appreciable quantities in the liver of twenty-four subjects. Ghigliotto [5] examined the organs of twenty-two persons dead of accidents. The zinc content (as zinc oxide) varied from 0.0015 to 0.0028 per cent of the viscera. Zinc was also found in the fetus.

Rost [12] has found among nonindustrial workers the presence of zinc in urine and feces. The average daily excretion in the urine ranges from 0.6 to 1.6 mg. (as zinc oxide) and in the feces varied from 9 mg. to as high as 39 mg. The source of the zinc is to be found in galvanized pipes, cooking vessels, cosmetics, etc. Salkowski [13] tested plum marmalade made in a zinc lined vessel. A zinc content of 3.4 per cent was found, estimated as the sulphate. Peterson, Haines and Webster [14] point out that milk, vinegar, soup and olive oil may be contaminated with zinc from storage in zinc containers. Some zinc is found in practically all foods. The zinc content in samples of beef, veal, pork and mutton ranged from 26 to 50 mg. per kilogram; in beef liver a maximum of 83 mg. per kilogram was found; in bread from 5 to 8 mg.; in dried vegetables 6.13 mg. and in cow's milk 3.9 mg.[12] Giaya [15] examined eight human subjects ranging from the unborn to 70 years.

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10. Bodansky, Meyer: Biochemical Studies on Marine Organisms, II, The Occurrence of Zinc, J. Biol. Chem. **44**:399-407 (Nov.) 1920.
11. Van Itallie: Normal Zinc, Arsenic and Copper Content of the Human Body, Nederl. Tijdschr. v. Geneesk. **63**:1709 (May 10) 1919.
12. Rost (Footnote 5, second reference).
13. Salkowski: Zentralbl. Biochem. u. Biophysiol. **19**:345, 1918.
14. Peterson, Haines and Webster: Legal Medicine and Toxicology, Ed. 2, Philadelphia, W. B. Saunders Company, 1923.
15. Giaya: Compt. rend. Acad. d. Sc. **170**:906, 1920.

Zinc was found in all. The amount increased in proportion to the age. His findings convinced him that zinc toxicity is lacking when stored zinc is less than 0.05 Gm. per kilogram of viscera.

In man the zinc content in milligrams per kilogram of tissue was found by Rost [12] to be: liver, 52 to 146; musculature, 47 to 52; brain, 11. Zinc workers excrete zinc long after they discontinue work in zinc industries. Rost believes that zinc may be absorbed through the intestinal tract, stored in the liver and muscles, and excreted in the urine, feces and milk. Salant, Rieger and Treuthardt [16] find that zinc is stored in considerable quantities in the liver.

From the foregoing it is obvious that the qualitative detection of zinc in human organs or excreta may be without significance. However, these data establish the storage of zinc in the human body, thus militating against the theory that zinc is harmless because it is not stored.

Mallory and Parker [4] have recently reported nephritis in animals due to the action of metallic zinc implanted subcutaneously. Schwartze and Alsberg [6] investigated zinc sulphate as an emetic. In the course of this work, intravenous injections of zinc sulphate brought about a gastric and intestinal inflammation. Salant,[17] after feeding rats weighing from 150 to 200 Gm. from 10 to 15 mg. of zinc acetate daily for four months, observed no impairments with the possible exception of renal disturbance. Sacher [18] reported that zinc fed rabbits developed albuminuria, renal congestion and gastric petechial hemorrhage. Brandl and Scherpe [19] fed zinc to animals and on necropsy observed hemorrhage into the gastric mucosa, renal congestion and cloudy swelling. Salant and Wise [20] introduced small quantities of zinc (10 mg. per kilogram of animal weight) directly into the circulation and noted as a result marked injury to the kidneys, nephritis and glycosuria leading to death in a few days.

Wherry [21] injected zinc acetate intravenously in dilutions of 1:20,000 of rabbit body weight. No manifestations developed in this experiment until the third day when the animal was found dead. A dilution of 1:32,000 per body weight was nonfatal. A higher con-

16. Salant, W.; Rieger, J. B., and Treuthardt, E. L. P.: The Distribution and Elimination of Zinc and Tin in the Body, J. Biol. Chem. **34**:463 (May) 1918.

17. Salant, W.: The Pharmacology of Heavy Metals, J. Indust. Hyg. **2**:72-78 (June) 1920.

18. Sacher, A.: Zur Kenntniss der Wirkung der Zinksalze, Arb. a. r. Pharmakol. Inst. zu Dorpat, **9**:88, 1893.

19. Brandl and Scherpe: Ueber zinkhaltige Aepfelschnitte nebst Versuchen über die Wirkung, des äpfelsäure zinks, Arb. a. d. k. Gsndhtsamte **15**:185, 1899.

20. Salant, W., and Wise, L. E.: The Production of Glycosuria by Zinc Salts, J. Biol. Chem. **34**:447 (May) 1918.

21. Wherry, W. B.: Regarding four unpublished experiments, 1922. Personal communication to the authors.

centration than 1:20,000 caused immediate death, or death within a short time. In the one case in which death followed a 1:20,000 dilution, on postmortem marked edema of the lungs was observed, a serohemorrhagic exudate into the peritoneal cavity, marked nephritis and swollen, gray kidneys with petechial hemorrhage. The stomach was not examined.

Application of zinc as treatment for cancer, particularly of the uterus, has led to absorption and systemic poisoning.

A skin disease attributed to zinc oxide powders has been found among workers in that chemical by Turner.[22] McCord and Kilker [23] have described ulcers on the extremities of workers in a wood preservation plant wherein zinc chloride was used as a fungicide.

Witthaus [24] enumerates fifty-nine deaths from the effects of zinc chloride, and twenty-nine from zinc sulphate. In all of these, the zinc salt was taken in error, or for suicidal purposes or given for homicidal purposes. Both the immediate and the late results center about the corrosive or irritant action on the intestinal tract. The lethal dose is not known because of the emetic action of these salts leading regularly to loss of at least part of the substance. The smallest known quantity of the sulphate causing death was 15.5 Gm.

Blyth [25] records the developments in a patient who died fourteen weeks after taking a tablespoonful of "Burnett's fluid," an aqueous solution of zinc chloride:

> There were at first violent vomiting and purging, but she suffered little pain, and in a day or two recovered sufficiently to move about the house; but the vomiting after food continued, everything being ejected about five minutes after swallowing. Before death she suffered from pneumonia. The stomach is seen to be much contracted—5 inches in length; it is ulcerated both near the pylorus and near the gullet; at the latter part there is a pouchlike portion of the mucous membrane of the stomach adherent to the spleen, which communicates by a perforation with an abscess formed and bounded by the stomach, diaphragm and spleen; it contained 3 ounces of dirty looking pus. At the pylorus, in the center, there is a second perforation, but extravasation of the contents is prevented by the adherent omentum and transverse colon.

In discussing sulphate of zinc Blyth states, "The infrequency of fatal results is due not to any inactivity of the salt but rather to its almost always being expelled by vomiting."

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22. Turner, J. A.: An Occupational Dermatoconiosis Among Zinc Oxid Workers, Pub. Health Rep. **36**:2727 (Nov. 4) 1921.

23. McCord, C. P., and Kilker, C. H.: Zinc Chlorid Poisoning, J. A. M. A. **76**:442 (Feb. 12) 1921.

24. Witthaus, R. A.: Manual of Toxicology, New York, William Wood & Co., 1911.

25. Blyth, M. W., and Blyth, A. W.: Poisons: Their Effects and Detection, London, Charles Griffin & Co., Ltd., 1906, pp. 690-692.

This review of the toxicology of zinc is not offered as a complete one. Sufficient is here included to convince that this metal has a greater toxicity than is commonly recognized by either zinc industrialists or physicians.

INDUSTRIES IN WHICH ZINC IS UTILIZED

We are listing below the major industries in which zinc in some form is found. This listing does not at all imply hazards to health in any degree or form. In some mentioned industries zinc poisoning is fairly common; in others, zinc poisoning is not known to have occurred, and in still others there are reasons to believe that zinc poisoning would not occur.

Processes involving the mining and smelting of zinc.
Processes involving the manufacture of brass and other zinc alloys.
Processes involving the manufacture of zinc salts and zinc oxid.
The galvanizing industry and sherardizing.
The rubber industry.
The paint industry.
The manufacture of oilcloths, linoleums, etc.
The manufacture of galvanic battery plates.
The manufacture of certain kinds of paper.
The desilverization of lead.
The manufacture of certain kinds of glass.
The manufacture of certain dyes and mordants.

INDUSTRIES IN WHICH ZINC IS UTILIZED

In two galvanizing plants in this locality we have studied workers and processes. In the first of these we have had a group of male workers under daily observation for three years. The number at work at any one time has not exceeded twenty, but on account of the high turnover the total number observed has been much higher. The men as a rule have been drinkers; have been users of tobacco to excess; have presented infected mouths; their eating habits have been bad, and their economic conditions have caused worry and stress. With a few exceptions, all workers are related by either blood or marriage. Most of the older men have been farmers and as a result present "weathered skins" and keratoses.

The work place is one room (45 by 45 feet) in which both pickling and galvanizing are carried out. The details of trade processes are recorded in another section. All work is done by hand. There are many openings in the roof and in the side walls. A large hood is in place above the zinc vat. Notwithstanding, fumes from the zinc vat and from the pickling tubs are visible. These tend to pervade the entire room and to mingle.

During the last three years those workers who have been longest employed (from five to twenty-two years) have come to us for the medical care of divers gastro-intestinal complaints. All histories suggested gastric or duodenal ulcers or hyperchlorhydria. Complete examinations were not possible on account of the fear or ignorance of these workers. Although some workers have passed out of this factory we have been able to see in those who have remained an increasingly severe condition, until it became imperative to investigate the cause.

The second plant is much larger. The work is limited to the galvanizing of sheets of metal and all is done by machinery. The workers do not come so closely in touch with materials used. The type of employee is the same. In this plant our personal observations have been limited to conferences with the plant physician and chemists, casual conferences with suspected workers, perusal of medical records, limited direct study of processes, analyses of blood, urine, dusts, etc. In this second plant we found evidences of acute zinc poisoning from "overheated metal," and of the dermatitis described by Turner [22] as caused by zinc oxid. We found the usual quantity of degenerative diseases, embracing divers cardiorenal and rheumatic conditions. We found, however, none of the gastro-intestinal conditions so common in Plant 1. The subsequent development of this material will supply a possible explanation of this difference.

TRADE PROCESSES INVOLVED IN THE PLANTS UNDER OUR OBSERVATION

In order that the presence of the substances potentially responsible for this occupational disease may be explained, the various steps in the galvanizing process are here detailed. "Galvanizing" is the term designating the coating of iron or steel with zinc. The first step is to prepare the material to be galvanized so as to present a clean metal surface, in order that it can "take" the coat of zinc. The cleansing of iron from adhering rust, scale or other foreign substances with acids is known as "pickling." There are several acids that may be used, sulphuric, hydrochloric, hydrofluoric. Sulphuric acid is the agent most commonly employed.

In Plant 1 the various tubs, buckets and cans to be galvanized are made from sheet iron. These sheet metal objects are placed in a large vat containing water and sulphuric acid. A gross rule of thumb governs the concentration and the temperature to be maintained. A solution of 7.5 per cent acid and a temperature of 150 F. probably represent optimal conditions. The sulphuric acid in this weak solution is not freely volatile, but it is sprayed into the air by rising bubbles and carried away by the steam arising from the vat. In the pickling process large vol-

umes of hydrogen are evolved. White [26] points out that as much as 1.05 cc. of hydrogen may be set free from every square inch of iron metal following pickling. This liberated hydrogen is capable of combining with the sulphur present as an impurity in the sheet iron, and with the arsenic found as an impurity in zinc.

After pickling the sheet iron objects are sometimes immediately submerged in molten zinc, but at other times are rinsed in dilute hydrochloric acid solution at room temperature. Some galvanizing plants allow for drying before submerging in molten zinc; others rinse in plain water, but in Plant 1 the object is submerged wet from the dilute acid.

The zinc chamber is roughly 4 by 8 by 3 feet in depth. Heating is obtained through the use of city gas, which is known to contain a small percentage of carbon monoxide. A flue for oven fumes extends up above the level of the workers' heads, emptying into a larger hood placed over the entire zinc chamber. The molten zinc is kept at a temperature of 468 C. The surface of the molten zinc is divided into two parts by a partition. On the surface of one part there is a superimposed layer of ammonium chloride that serves as a flux. In addition to ammonium chloride used in this step, admixed zinc chloride is often used. Mixed with the ammonium chloride are small quantities of "cereal middlings" to fluff it up. From time to time during the day, there is placed into the molten zinc small bars of a commercial combination of metals called "silver metal." This serves as a brightener for the galvanized surface. This "silver metal" contains aluminum and tin. Several workers stand directly over the molten zinc. These workers are engaged in submerging and lifting out articles to be galvanized. The work is at a high temperature at all seasons. The galvanized articles are allowed to drip free of molten metal and after a few minutes are removed for stripping of adhering particles and for storage.

The foregoing processes for galvanizing hold true in a general way for all plants galvanizing small articles, cans, tubs and such utensils. In the second plant, the galvanizing is limited to flat sheets of metal. All sheets are of the same size and essentially all processes are carried out by machinery. Instead of recounting in detail the trade processes involved, only items different from those described above will be mentioned. In the latter plant, after pickling by machine dipping, all sheet metal is redipped in lime water to neutralize the acid. Although vapors arise visibly from both of these kinds of vats, there is no obvious mingling of fumes until far above the breathing level of workers. These vats are some distance away from the molten zinc vats in which

26. White, G. A.: A Metallurgical Study of the Steel Base as Related to Galvanizing, Buffalo, Matthews-Northrup Works, 1918.

no intermingling of fumes is noticeable at low levels. Prior to submersion in molten zinc a dipping is made into ordinary water. It is believable, therefore, that no gross distillation of zinc chloride or zinc sulphate takes place at this point. Other differences of lesser import have been noted, such as the use of tallow as the fluffing agent instead of middlings, and the blowing of sulphur dioxide fumes over the surface of the molten zinc. In this second plant no "silver metal" is used.

It has already been noted that in Plant 2 no cases of the occupational disease under study have arisen. It is believable from analyses made that the same impurities of crude materials are common to each plant. The type of workmen is similar although no "old timers" are found in Plant 2, owing to past labor difficulties. The following differences in the processes involved may serve to explain the difference in health conditions:

Plant No. 1	Plant No. 2
1. The workroom is small, with low ceiling and visible mingling of fumes.	1. The workroom is large, with the ceiling 65 feet above ground level, with mingling of fumes only at high levels.
2. The pickling and galvanizing vats are placed relatively close together, favoring the admixture of fumes.	2. Vats for pickling and galvanizing are at a greater distance.
3. All work is done by hand with men in close proximity to chemicals employed.	3. All work is done by machinery, with the men kept at considerable distance.
4. Pickled objects, wet with acid, are submerged directly in molten zinc through flux of ammonium chloride.	4. Pickled objects are submerged in lime water to neutralize the acid and later into tap water, prior to submerging in molten zinc through flux of ammonium chloride.
5. The majority of the workers have been employed in excess of six years.	5. Practically all the workers have been employed less than six years.
6. "Silver metal" is used.	6. "Silver metal" is not used.

ANALYSES OF MATERIALS AND DUSTS [27]

Since, in our opinion, exposure over long periods of time is necessary to develop the condition being studied, not a great deal of information is to be gained from analyses of materials used at this immediate time. Materials in use in the course of twenty years have been obtained from different sources, made by different processes, without doubt containing varying quantities of impurities. Analyses have been made, however, on some materials. In other instances acceptable recorded analyses have been utilized. It is our purpose in recording these analyses to indicate the general character of impurities.

The sheet iron, later to be galvanized, presented the following impurities: carbon, manganese, sulphur and phosphorus. The quantity of these impurities varies. According to White,[26] the percentage is approximately: carbon, 0.13 per cent; manganese, 0.38 per cent; sulphur, 0.04 per cent; phosphorus, 0.065 per cent.

27. A portion of the analytic investigation was conducted by the Langdon-Meyer Laboratories, Cincinnati.

Analysis of the substance (Klean-rite) which is placed into the sulphuric acid to facilitate pickling indicated 98 per cent commercial sodium chloride and 2 per cent organic material.

The ammonium chloride tested 98 per cent pure ammonium chloride.

Analyses of spelter by Ingalls [28] are accepted by us as representing the average spelter in use. One analysis is here cited, showing the impurities mixed in with the zinc.

Lead	Iron	Cadmium	Arsenic	Antimony	Copper	Bismuth	Silicon Oxide	Sulphur	Carbon
0.0701%	0.7173%	.....	0.0603%	0.0249%	0.1123%	.....	0.0346%	0.0035%	0.1775%

The sulphuric acid in current use tested 76.9 per cent. Traces of lead were found. Negligible traces of unrelated impurities were detected.

Analyses of dust settlings taken from ledges near the galvanizing vat in Plant 1 were made on several occasions, of which two are cited:

Analysis 1—Qualitative

A sample of the dust settling above the galvanizing pot and representing probably the condensable portion of the fumes to which the operator is subject shows a trace of antimony, much zinc, iron, sulphides, sulphates and chlorides, as well as some material insoluble in strong boiling acids.

Analysis 2—Limited Quantitative Analysis

	Per Cent
Sulphur as sulphates (SO_3)	14.20
Iron and aluminum oxides	8.92
Zinc as Zn	35.00
Ammonia as NH_4	6.25
Chlorides, Cl_2	18.50
Sulphur as sulphide	0.08
Calcium	traces
Arsenic	doubtful traces

In Plant 2, a specimen of ledge dust was taken at a level of about 45 feet above the heads of the workers. The analysis exhibited constituents as follows:

	Per Cent
Sulphur as sulphates (SO_3)	17.29
Iron and aluminum oxides	6.65
Zinc as Zn	45.5
Ammonia as NH_4	10.35
Chlorides as Cl_2	13.36
Hydrogen sulphide	0.06
Lead	traces
Tin	traces
Water soluble material	55.32
Antimony	0
Arsenic	0

A qualitative analysis of "spelter dross" revealed zinc, iron and aluminum, together with doubtful traces of arsenic.

In the galvanizing room of Plant 1, zinc oxide comes into contact with sulphuric acid in the presence of moisture. The combination of these two substances leading to the formation of zinc sulphate is regarded by us as a certainty. Similarly, the combination of zinc oxide with hydrochloric acid leads to the formation of zinc chloride. One of

28. Ingalls, W. R.: Metallurgy of Zinc and Cadmium, Eng. & Mining J., London, 1903.

the consulting chemists aiding us on this point sought to determine the precise amount of these zinc salts through methods based on the measurement of the total amount of molecular material available for combination. The figures indicate the presence of zinc sulphate in the ledge dusts of Plant 1 to the extent of 15 per cent, and zinc sulphide to the extent of 0.72 per cent. Other chemists accept with certainty the presence of zinc sulphate, zinc chloride and zinc sulphide, but recommend the avoidance of fixing any precise percentage. Thorpe [29] attests to the formation of zinc chloride under the conditions mentioned:

> The ammonium chloride, used as a flux in galvanizing, is gradually lost during the process, and fresh additions have to be made as required. This loss is doubtless due in part to volatilization of the salt itself, but also to a reaction which takes place whereby zinc chloride is formed and ammonia set free.

From these analyses, recognition must be given to a number of potentially harmful substances, such as hydrogen sulphide, arseniureted hydrogen, arsenic, mineral acids, ammonia, ammonium chloride, lead, antimony, cadmium, aluminum, zinc, zinc oxide and zinc salts.

A faithful consideration of these potential hazards leads us to the attachment of greater significance to the zinc salts accidentally formed as described in the foregoing. We are influenced in this tentative decision by the results of earlier cited animal experiments, wherein chemically pure zinc or zinc salts have been utilized. It is impracticable to incorporate here all the consideration given to the other potential intoxicants. The general trend of our consideration of these other substances is indicated in the items now cited. Concurrent with this series of galvanizing cases we have studied a group of lead cases from a storage battery plant. The manifestations have been markedly dissimilar in these groups, except in the anemia and constipation present. Using the method of McCord, Minster and Rehm for the detection of basophilic material, large amounts of this substance have been found in all but one of our lead cases, while in the series of galvanizers only one of those tested has exhibited large amounts of basophilic material. From the consideration of cadmium as a possible cause, it is to be pointed out that this metal is so volatile that it is almost entirely eliminated in zinc smelting. If this were the producing agent, the disease under study might be expected to be more prevalent among zinc smelters. Arsenic, of course, must be considered since this material is present as "traces" in our analyses. In chronic arsenic poisoning the absence of arsenic pigmentation of the skin is unusual. Other characteristics, such as "arsenic pock," paralysis of muscles and peripheral neuritis are fairly constant. If our cases were attributable to arsenic surely some

29. Thorpe, T. E.: Dictionary of Applied Chemistry **5,** New York, Longmanns Green & Co., 1913.

percentage of our patients would present these outstanding characteristics of arsenic poisoning. In a similar manner the other potentially harmful substances have been studied and tentatively ruled out as producers of the entire symptom complex. We are, however, receptive to the idea that where so many potential hazards exist "mixed poisoning" may occur.

REPORT OF CASES

CASE 1.—A man, aged 37, who had been a galvanizer for about twenty years, Feb. 5, 1924, consulted us because of "stomach trouble," which had been present for several months. He had had one severe attack of pain in the epigastric region. For several weeks he had had a burning pain in the epigastrium, beginning two or three hours after meals. This pain was relieved by food. There was occasional vomiting of "coffee grounds" vomitus. He had marked constipation and frequent severe headaches, but no knowledge of blood in stools. A limited examination at that time established tenderness in the epigastrium. The patient declined treatment. June 7, 1924, the patient consulted us on account of a severe epigastric pain. Treatment was again refused. May 2, 1925, the patient submitted to a limited examination and treatment.

The history taken and the examination made at that time revealed that the patient had been essentially well until the present illness. For a long time he had had palpitation of the heart and continuous constipation. He had had a gonorrheal infection two or three times during his life. He had frequent toothaches in various teeth.

In the past he had taken whisky three times a day, beer three times a day, and coffee three times a day. He now drinks moonshine, and at times becomes thoroughly drunk.

He had begun work as a newsboy at the age of 10 years. He was a sandpaperer of heels in a shoe factory at the age of 15 years. At about 17 years he began his present employment, at first as a porter, but he soon "went on kettle," where he remained until the present time.

His best weight was 135 pounds (61.2 Kg.) with an average of 130 pounds (59 Kg.). His present weight was 130 pounds. His height was 5 feet 8 inches (172.7 cm.). He was a fairly well developed, poorly nourished adult of rather poor intelligence.

The skin showed a marked pallor; the lips were of poor color, and the skin was scarred by metal burns. Numerous metal burns appeared around the face and neck. No eruptions, small pigments, moles or nevi were noted, and no marked myotatic irritability.

The eyes reacted to light and distance, and the extra-ocular movements were normal. Astigmatism was present. An ophthalmoscopic examination was negative. The disk outlines were sharp. There were no hemorrhages. The arteries were not contracted.

The teeth were in poor condition; there were several bad roots and slight pyorrhea but no lead line. The tongue protruded in the midline without a tremor. The tonsils and pharynx were negative.

The inguinal glands were palpable, but the rest of the glands were negative.

The chest was slightly flat. Expansion was symmetrical and fairly equal on both sides. There was retraction at both apexes, greater on the right.

On percussion the lungs showed hyperresonance throughout, with hyperresonance over the heart area, the base posteriorly five fingers below the lower border of scapula. Breath sounds were increased over the entire chest. No râles or friction rubs were heard.

Relative cardiac dulness was 3.5 by 10 cm. and retrosternal dulness 6.5 cm. The first sound was snappy at the apex. At the base a soft systolic murmur was heard over both areas, which was not transmitted up. There was a suggestion of sinus

arrhythmia of the respiratory type. The cardiac rate was 100. The systolic blood pressure was 132, the diastolic 92. The temperature was 97.2.

The abdomen was below the chest level. The liver edge was not felt. There was distinct epigastric tenderness, which was distinctly localized. Apparently a contracted wall of the colon could be felt (rolled under the finger).

The reflexes were slightly increased. There was no Babinski reflex. The biceps reflex was double plus.

Blood examination, May 9, 1925, revealed hemoglobin, 80 per cent; red blood cells, 3,200,000; white blood cells, 5,800; polymorphonuclear leukocytes, 62 per cent; small lymphocytes, 35 per cent; large lymphocytes, 2 per cent, and transitionals, 1 per cent. The Wassermann reaction was negative. Urinalysis, May 14, showed a volume of urine of 350 cc. said by the patient to be a twenty-four hour output. Zinc (as Zn) was 0.35 Gm. per liter.[30] June 9, the volume of urine was 970 cc. in twenty-four hours; it was acid to litmus and negative for bile. The sulphates were 1.89 Gm. per liter; chlorides (Cl_2), 1.42 Gm. per liter; iron and aluminum oxides, 0.525 Gm. per liter. There were slight traces of tin. Zinc (as Zn) was 0.189 Gm. per liter. There were slight traces of albumin; it was negative for sugar and for blood. The patient was not working at time of either urinalysis.

Roentgen-ray examination showed evidence of two ulcers, one duodenal and one pyloric.

CASE 2.—A man, aged 40, at present an inspector of galvanized products, from 1903 to 1910 was a galvanizer; from 1910 to 1918 worked in the lead industry; from 1918 to 1923 was a galvanizer, and from 1923 to 1925 an inspector. He stopped galvanizing two years before examination because of an ulcer of the stomach, diagnosed and treated by his family physician. June 2, 1925, the patient gave a history of being on a rigid diet for irregular periods, the chief foods being milk and eggs. Continuous tenderness was present over the epigastric region with pain radiating to the right and to the left. There were tarry stools at frequent intervals, with occasional fresh blood to the extent of 3 or 4 spoonfuls in a stool.

On examination the patient was found to be somewhat undernourished. He was pale, and there was a grayish brown tinge to the exposed portions of the skin. There were a few scars from galvanizing on the exposed parts of the skin. The patient exhibited the usual characteristics of unhealed, persistent ulcer.

Blood examination, June 6, 1925, revealed hemoglobin, 80 per cent; red blood cells, 3,470,000; white blood cells, 5,200; polymorphonuclears, 69 per cent; large lymphocytes, 4 per cent; small lymphocytes, 26 per cent, and myelocytes, 1 per cent.

Roentgen-ray examination did not establish ulcer.

After conference with the patient's family physician a diagnosis of ulcer was accepted.

CASE 3.—A man, aged 32, a galvanizer for twelve years distributed over a period of seventeen years, had worked at five different galvanizing plants, always doing hand work.

Five years before examination, the present difficulty started with belching of gas and sour stomach. The condition had become slowly worse since that time. Three years before he had attacks at about six week intervals of severe abdominal pain with vomiting and inability to eat most foods. Between attacks, a dull pain was continuously present. At times he was unable to work, and he was continuously dizzy.

Vomiting had been a constant feature. The vomitus was described as being at times "coal black"; at other times greenish, containing clots of blood. Fre-

30. Quantitative urinalyses for zinc were carried out by the wet incineration method after evaporation of the urine to a small volume. After separation of other metals, zinc was precipitated by hydrogen sulphide. The zinc was weighed as $Zn_2P_2O_7$ and calculated as metal zinc. This method is subject to possible error. The analyses were made by F. J. Andress, University of Cincinnati.

quently, there had been periods when "tarry" stools were regular. The patient was in the hospital three years before on account of "stomach trouble."

At the present time the patient complained of pain in the epigastrium and also just inside the right iliac crest. During the last month there had been three attacks of severe pain with vomiting. At times he was able to eat any food except "sours." When the pain was severe, practically all food was vomited except chilled milk. Baking soda at times caused vomiting. At times the eating of food stopped pain; at others the pain was increased by food; and at still others relief came about two hours after eating.

The examinations made were without significance except in the following respects: Moderate abdominal tenderness was present around the umbilicus, in the right iliac fossa and beneath the xiphoid. No rigidity and no masses were noted. Roentgen-ray examination established some inconclusive evidence of postpyloric ulcer although clinically the condition was regarded as gastric ulceration.

Blood examination revealed hemoglobin, 90 per cent; red blood cells, 3,690,000; white blood cells, 6,750; polymorphonuclears, 68 per cent; small lymphocytes, 29 per cent; large lymphocytes, 3 per cent, and basophilic aggregation test, 2 plus.

Urinalysis indicated normal urine without any evidence of impaired renal function; a qualitative test for zinc was positive.

CASE 4.—A man, aged 58, worked as a galvanizer for sixteen years, doing all the jobs connected with galvanizing. He quit work as a galvanizer five years before examination because of "stomach trouble." There was no record in the case of alcoholism or excessive use of tobacco.

Previous to doing galvanizing work the patient was exceptionally well. This continued for eight years after he began galvanizing. The patient first suffered from nausea, distention and gastritis. Two years after the onset the condition became severe, necessitating absence from work for considerable periods. There was pain over the entire abdomen radiating upward, over the lower ribs and in both axillary lines. The pain was sufficiently severe to prevent sleeping. He vomited almost daily. Baking soda gave relief but foods afforded relief only at times. "Tarry" stools were not observed. There was no diarrhea and no constipation. Headache over the top and front of the head was fairly constant. During the years of abdominal disturbance the patient also suffered from a dermatitis which he attributed to the chemicals employed.

After six years of attempting to work with this abdominal condition, the patient quit and became practically an invalid for two or three years. During the last three years the patient had been doing farm work, which had been his occupation prior to his becoming a galvanizer.

At the present time he vomits a great deal, at least on an average of three days a week. Occasionally he has severe attacks of pain and vomiting, lasting two or three weeks. Baking soda gives some relief. The vomitus is sour, but not of "coffee grounds" type; it contains food. The patient eats practically all foods but states that many do not agree with him.

CASE 5.—A man, aged 29, a galvanizer for about seven years, was said to have more severe trouble than any other worker, but refused all cooperation. Other members of the family and fellow workmen were consulted. The condition had begun about one year before the investigation as "stomach trouble." He had lost considerable time owing to the condition, was unable to eat, and had several severe attacks. He was now on a meat-free diet. No direct history was taken by us, no examination was made, and no diagnosis.

CASE 6.—A colored man, aged 29, who was employed in a third plant never inspected by us under unknown work conditions, had worked at galvanizing for seven years. He had done pickling as well as all "jobs around the kettle." He was first seen, Nov. 13, 1924, on account of zinc chills, probably associated with lead poisoning; he recovered.

June 1, 1925, he discontinued work and became a truck driver, leaving the galvanizing work because of increasing impaired health. During the previous six

months he had had five severe attacks of abdominal pain, which came on at night and which were relieved by baking soda or by drawing up the limbs tight across the abdomen. He was unable to eat many kinds of food, particularly acid foods and meat. In addition to severe attacks of pain, there had been a fairly continuous dull pain in the abdomen, and there were intermittent severer pains in the abdomen between meals. The patient was constipated at times. This increased the severity of the abdominal pain. No tarry stools and no vomiting were noted, but there was some belching of gas and distention of the abdomen at intervals.

CASE 7.—A man, aged 51, a galvanizer for eighteen years with an aggregate loss of one year during the eighteen, two years before examination developed "stomach trouble." He was on a strict diet for nine months. The pain was located over the epigastrium and in the back of the left side. There was a low grade ache in the abdomen, with patient having occasional severe attacks. He was markedly constipated and the abdominal pain was worse when he was constipated. The pain was more noticeable between meals; eating was known to relieve the pain. He felt no pain at night, provided he ate supper. At the present time he was on a strict diet.

The routine examination of the patient was without significance except in the following respects: The patient, who was large framed and muscular, presented a pale skin and pale mucous membranes; exposed portions of the skin were of brownish tinge with keratoses. There was distinct tenderness in the abdomen, well localized over the duodenal region.

Blood examination revealed: hemoglobin, 80 per cent; white blood cells, 5,600; red blood cells, 3,960,000; polymorphonuclears, 61 per cent; small lymphocytes, 34 per cent; large lymphocytes, 3.5 per cent; transitionals, 1 per cent; myelocytes, 0.5 per cent, and basophilic aggregation test, 6 plus.

Examination of the urine revealed: total volume 870 cc.; it was acid to litmus and negative for bile. Sulphates (SO_3) were 1.162 Gm. per liter; chlorides (Cl_2), 4.43 Gm. per liter; iron and aluminum oxides, 0.176 Gm. per liter, and zinc as Zn, 0.31 Gm. per liter. There were traces of albumin; it was negative for sugar and blood; there were traces of lead.

Roentgen-ray examination established bilateral fibrosis of the lungs and marked gastric hyperperistalsis. The stomach and the duodenum were of regular contour.

In this case we are convinced that lead was a contributory factor. Examination of the blood showed an excess of basophilic material. Traces of lead were found in the urine, and clinically there was a record of long standing rheumatism of a character suggesting lead arthritis.

CASE 8.—A man, aged 46, a galvanizer for about twelve years, had worked "off and on" for galvanizer employers during a period of twenty-two years. He did night work. The present condition began about one year before examination. This was first a nausea which was severe enough to cause loss of time from work. Pain in the abdomen became sharp in character, and was more severe before meals, particularly before the evening meal, following a day of sleep. Food at once relieved pain. Constipation aggravated the condition.

At the present time there were no remissions except when he was away from work for two or three days, when the condition became less severe. There was marked distention of the abdomen at frequent intervals but no belching of gas. The patient had noted "coal colored" stools and dark colored urine.

CASE 9.—A man, aged 38, for fourteen years had been a galvanizer with his present employer; for seven years he had done dipping. The general history was without significance except that he had been a heavy drinker of beer. Years before the examination he had had malaria. Since he had been galvanizing he had suffered from eye strain, headaches, and blurring associated with headaches. His best weight was 160 pounds (72.6 Kg.), with an average of 155 pounds (70.3 Kg.); his present weight was 154 pounds (69.9 Kg.).

About a year and a half before examination "stomach trouble" developed. This was not well defined until about eight months before, when he began to feel a dull ache in the pit of the stomach. This pain would appear two or three hours after eating and would continue until the next meal was taken or until some food was eaten. The eating of food always relieved the pain. This "ache" in the stomach was usually accompanied by the belching of gas and sour eructations, occasionally by nausea. The patient gave no history of having vomited, nor had he noticed anything unusual about his stools. The abdominal pain mentioned varied from what the patient called a "dull ache" or "hungry feeling" to a fairly sharp pain, which never was so severe as to double him up. Occasionally, a dizziness occurred, especially on reclining or tipping the head backward. In the morning there was a foul taste in the mouth although the appetite for breakfast was fair. At no time had the eating of food caused the patient any distress. There were no diarrhea, no constipation and no recognized intestinal pain. At no time were there remissions represented by weeks or months.

CASE 10.—A man, aged 66, a galvanizer for eighteen years, now doing other work or no work, was in a state of mental confusion due to alcohol.

This patient gave a typical ulcer history with pain so severe that many nights he lay doubled across a board fence. He had severe attacks at least once a month for many years. The patient was of the opinion that the condition started prior to the beginning of galvanizing work. A history was obtained in a local hospital suggestive of ulcer. No great significance was attached to the patient's statements.

CASE 11.—A man, aged 38, a galvanizer for about eight years, with some irregularity in his work, two years before examination developed distention of the abdomen, noticed particularly in the morning before breakfast. Later this was associated with nausea and later with abdominal pain. The pain was more severe when the patient was constipated. He had "heartburn" and had lost some weight. The pain was localized in the right iliac region and over the epigastrium. There was tenderness on pressure. Alkalis gave immediate relief. An ulcer diet had led to marked improvement.

Details of the physical examination made are omitted except the following laboratory findings:

A blood count, May 9, 1925, revealed: hemoglobin, 70 per cent; red blood cells, 2,770,000, and white blood cells, 7,050. An after-treatment blood count, June 6, revealed: hemoglobin, 75 per cent; red blood cells, 3,440,000; white blood cells, 8,000; polymorphonuclears, 67 per cent; small lymphocytes, 28 per cent; large lymphocytes, 4 per cent, and myelocytes, 1 per cent.

Urinalysis revealed: total volume, 850 cc.; it was acid to litmus and negative for bile. Sulphates (SO_3) were 2.86 Gm. per liter; chlorides (Cl_2), 4.75 Gm. per liter; iron and aluminum oxides, 0.656 Gm. per liter. There were traces (distinct) of zinc as Zn. It was negative for albumin and sugar, and gave doubtful traces of blood.

A roentgen-ray examination was without significance.

Case 12 is cited as an example of a group coming under our observation in which the patient was not so severely afflicted as to be classed with the foregoing.

CASE 12.—A man, aged 34, had been an irregular galvanizer since 1908; his present employment began five months before examination; he worked on the night shift. After working three and one-half months the patient developed what he termed indigestion. He noted that various foods, particularly fruits, onions and cucumbers, caused abdominal distress. He had distention of the abdomen, with severe cramps. The pain was located around the umbilicus.

The pain at the present time was essentially constant. Foods made the pain worse. Constipation increased the pain. Relief was obtained by expelling gas.

At times he belched particles of food, and said that he belched up materials that put his "teeth on edge"

Case 12 is representative of a group of employees at work for shorter periods, from six months to five years, including one man who "off and on" had worked during twelve years. Only two men who had worked in excess of eight years were free of abdominal disease.

The high incidence of gastro-intestinal disease in this group under observation is much in excess of what is true for this type of person in industry in general. In Plant 1, of more than 200 workers in departments other than galvanizing, only one gastric or duodenal ulcer has been detected in three years.

We are well aware that in our examinations much helpful information has not been obtained. The type of worker has almost entirely precluded such tests as gastric analyses. Notwithstanding the absence of these desirable diagnostic aids, we are of the opinion that several of these workers have gastric or duodenal ulcers, certainly gastric or gastro-intestinal inflammation to a severe degree.

SUMMARY

In a small galvanizing plant, we have detected widespread gastro-intestinal conditions, varying from gastro-enteritis, in the younger workers, to well established gastric and duodenal ulcers among workers employed for a long time. Twelve out of fifteen workers employed seven years or longer have presented severe gastro-intestinal lesions.

In a second plant, in which all employees are new at this work (less than six years) and in which the general work conditions are better and exposure to trade process fumes is much less, no cases of this gastro-intestinal disease have been found.

We have shown the accidental formation of zinc sulphate and zinc chloride at levels and under conditions that involve exposure on the part of the workers in Plant 1.

In all workers whose urine has been tested, zinc has been found in quantities in excess of the accidental urine content from food, galvanized iron pipes, etc.

These patients have not presented the characteristics of other occupational disease hazards attending galvanizing.

We have sought to stress the occurrence of multiple hazards in the galvanizing industry. On this account we feel unwarranted in drawing any precise conclusions as to the etiologic factor in these cases. Althought we attach significance to zinc as a causative agent, we accept various other substances as possible contributing factors. We also believe that the unhygienic conditions of the work place, together with

the physical type of worker, favor the occurrence of the conditions we have described.

A close resemblance is seen between our observations of lesions among zinc workers and the findings in the literature referred to in which study has followed the administration of single, chemically pure substances. Our concept that zinc is capable of producing chronic systemic poisoning is aided (*a*) by the work of Mallory and Parker in obtaining kidney lesions from pure metallic zinc implanted subcutaneously, thus disproving the often repeated statement that metallic zinc is nonpoisonous; (*b*) by the work of several authors establishing stored zinc in appreciable quantities in various organs and tissues and in excreta of zinc workers, long after the discontinuance of zinc work; (*c*) by the creation of alimentary tract lesions by pure zinc salts administered intravenously and by mouth.

A long period of time expressed in years (from five to twenty) appears necessary for the production of the lesions described.

34 West Seventh Street.

THE BLOOD IN SMALLPOX DURING A RECENT EPIDEMIC*

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HISTORICAL REVIEW

Brouardel is generally referred to as the first investigator who made studies of the blood in smallpox. In 1874 he published his observations on the behavior of the leukocytes in this disease and emphasized the presence of a leukocytosis "during the febrile remission between the period of eruption and of suppuration. He found them diminished during suppuration, an increase at this time or during desiccation signifying to him secondary pyogenic infection." [1]

Corroboration of these findings and additional observations, particularly the studies of the morphologic changes of the leukocytes and the differential count, were made by a number of men; notably, Pick (1894), Rogers (1900), Courmont and Montagard (1900), Weil (1901), Ferguson (1902), Perkins and Pay (1903), Magrath, Brinkerhoff and Bancroft (1904), and others. Kammerer (1910) and Erlenmeyer (1913) and, more recently, Pantasis (1924) reviewed the literature extensively and reported the analysis of their own findings. Schilling, during an epidemic of moderate severity in eastern Galicia during the war, and Hoffman, during an epidemic of mild cases in Havana in 1921, made similar studies.

There is an essential agreement among these observers as to the findings of major import in the blood in smallpox. These may be briefly summarized as follows:

There is, as a rule, a leukocytosis in all forms of smallpox and the degree of leukocytosis seems to be in direct proportion to the severity of the disease.

The uncomplicated discrete form may show little variation in the total leukocyte count throughout the course of the disease.

Occasionally, severe forms may show persistent leukopenia.

Hemorrhagic and purpuric cases usually show a persistent hyperleukocytosis.

There is a relative decrease in the neutrophilic leukocytes.

The mononuclear cells are definitely increased both relatively and absolutely.

Pathologic forms, such as the so-called "stimulation" or "irritation" forms, plasma cells, atypical lymphocytes, myelocytes, metamyelocytes and Arneth's young leukocytes are frequently found.

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* From the pathologic laboratory of the Minneapolis General Hospital.

1. Magrath, G. B.; Brinkerhoff, W. R., and Bancroft, I. R.: The Leukocyte Reaction in Variola, J. M. Res. **6**:247, 1904.

The erythrocyte count and the percentage of hemoglobin are little affected except in severe pustular or protracted cases.

Normablasts, polychromatophilia and anisocytosis are found in severe cases, and certain structural changes of leukocytes, such as the vacuolization and bluish discoloration of the cytoplasm and the condensation and fragmentation of the nucleus, also may be present in hemorrhagic cases.

There is, however, no consistent agreement among the writers who attempt to correlate various total leukocyte and differential counts with the days of the disease.

Relative frequency of certain cells, such as myelocytes, large mononuclear leukocytes and eosinophils at various stages of the disease also is in dispute.

As to the practical value of the blood findings in the early diagnosis and prognosis of smallpox, opinions also differ. Many seem at least

TABLE 1.—*Smallpox Patients Admitted to the General Hospital from March 1, 1924, to Feb. 28, 1925, Together with Figures for the Entire City of Minneapolis, the State Outside Minneapolis, and the Entire State.*

	Cases	Percentage	Deaths	Percentage	Percentage of Total
Discrete pustular (mild)	191	39.8	10	5.2	2.1
Confluent pustular (severe and fatal)	110	22.9	55	50.0	11.5
Hemorrhagic pustular (severe and fatal)	131	27.3	106	80.9	22.1
Purpuric (fatal)	48	10.0	48	100.0	10.0
Total	480	100.0	219	44.0	
Percentage of all the city cases (1,276)		37.6		66.0	
Entire city	1,276	40.4	332	26.0	14.7
State (outside Minneapolis)	1,892	59.6	105	5.5	3.3
Entire state	3,168		437	13.8	

skeptical, while others (Weil, Courmont and Montagard, Erlenmeyer and Hoffman), consider them of practical importance. Few, if any, however, would seem to venture a definite diagnostic or prognostic significance in given findings without some clinical data.

It is to be noted also that the majority of the writers base their conclusions on the studies of a comparatively small series of cases (Pick, forty-two cases; Rogers, thirty-six cases; Courmont and Montagard, twenty-nine cases; Weil, twenty-four cases; Schilling, twenty cases; Pantasis, twenty cases). Their findings and conclusions would therefore seem of value, mainly, so far as they confirm the observations of other investigators.

ANALYSIS OF 250 EXAMINATIONS

An analysis of the results obtained from the examinations of the blood in approximately 200 cases of smallpox, representing all forms and stages of the disease during the recent epidemic in Minneapolis (Table 1), confirms, in the main, the findings of the men just summarized. There are, however, certain additional findings of definite

value which may further serve as an aid in the diagnosis and prognosis of this disease.

I may state here, parenthetically, that the difference between the blood findings of all the frank pustular forms and those of the purpuric form [2] is so strikingly constant that it seems necessary to record them separately in the following presentation.

THE PLATELETS (TABLE 2, FIG. 1)

Simon [3] mentions the behavior of the platelets in smallpox in these words, "There is a great diminution of platelets during the febrile period and a material increase during the pustular stage." It is generally known that, in smallpox as in pneumonia, measles and certain

TABLE 2.—*Findings in Various Types of Smallpox*

		Platelets			Total Leukocytes			Polymorphonuclears			Temperatures		
Stage*	Cases	Highest	Lowest	Average	Highest	Lowest	Average	Highest, per Cent.	Lowest, per Cent.	Average, per Cent.	Highest, Degrees	Lowest, Degrees	Average, Degrees
Mild Pustular Form													
1	3	103,500	85,000	91,100	19,000	3,000	10,000	79	60	71	102.4	100.0	101.2
2	12	90,000	10,000	49,000	9,700	3,100	5,883	79	28	40	103.8	98	99.9
3	9	65,000	15,000	36,100	26,000	5,500	13,200	76	39	56.4	101.8	98.8	99.9
4	7	185,000	12,000	74,950	28,000	15,900	20,923	69	57	61.4	102.0	97.6	100.5
5	19	300,000	100,000	174,250	33,000	7,550	14,630	62	17	47	101.2	96.8	98.4
Severe and Fatal Pustular Forms													
1	6	75,000	35,000	51,660	21,000	7,700	13,700	88	75	83	103.8	99.4	101.8
2	16	75,000	8,000	31,368	31,340	8,000	13,024	89	75	82	106	102.2	103.5
3	19	62,000	6,500	25,450	33,000	6,000	14,700	93	53	66.7	103.8	99.4	102.4
4	9	160,000	45,000	98,818	31,500	13,500	17,950	70	54	62.7	103.6	97.0	100.4
5	15	350,000	115,000	184,630	37,800	11,500	22,636	84	41	70	104.2	97	100.5
Primary type† Purpuric Forms													
1	13	72,000	11,000	36,300	37,000	4,400	21,600	73	10	39	103.2	98.2	100.3
2	9	65,000	15,500	32,750	52,000	11,000	26,336	57	6	28	100.4	97.2	99.8
Secondary type†													
1	8	35,000	8,000	23,150	31,340	9,000	14,500	88	52	76	103.6	99.6	102.6
2	8	62,500	7,500	23,750	21,500	11,500	16,070	79	38	64	105	99.4	102.3
3	7	20,000	5,000	13,500	30,600	4,600	15,431	73	8	40.6	102.3	98	99

* 1, preeruptive; 2, maculopapular; 3, vesicular; 4, pustular; 5, desiccation.
† 1, first two days; 2, second three days; 3, last three days.

other infectious diseases, there is a low platelet count at the onset. Beyond this fact, no further studies appear to have been undertaken by investigators with reference to the various forms of smallpox.

In the initial period of the mild form of pustular smallpox, an average platelet count is 91,100 per cubic millimeter (highest, 103,500; lowest, 85,000). This is followed by an average of 49,000 per cubic millimeter (highest, 90,000; lowest, 10,000) in the maculopapular period and of 36,100 per cubic millimeter (highest, 65,000; lowest, 15,000) in the vesicular stage. From this point it shows a steady rise through the pustular stage, when an average count is 74,950 per cubic

2. Ikeda, Kano: The Blood in Purpuric Smallpox with a Clinical Review of Forty-Eight Cases, J. A. M. A. **84**:1807 (June 13) 1924.

3. Simon, C. E.: Clinical Diagnosis, Ed. 9, Philadelphia, Lea & Febiger, 1916, p. 827.

millimeter (highest, 185,000; lowest, 12,000), into the desiccation period, with an average of 174,250 per cubic millimeter (highest, 300,000; lowest, 100,000). Practically the same course is followed in the severe and fatal pustular forms: The initial period is 51,660 per cubic millimeter (highest, 75,000; lowest, 35,000); the maculopapular period, 31,368 per cubic millimeter (highest, 75,000; lowest, 8,000); the vesicular stage, 25,450 per cubic millimeter (highest, 62,000; lowest, 6,500); the pustular stage, 98,818 per cubic millimeter (highest, 160,000; lowest, 45,000), and the desiccation period, 184,630 per cubic millimeter (highest, 350,000; lowest, 115,000).

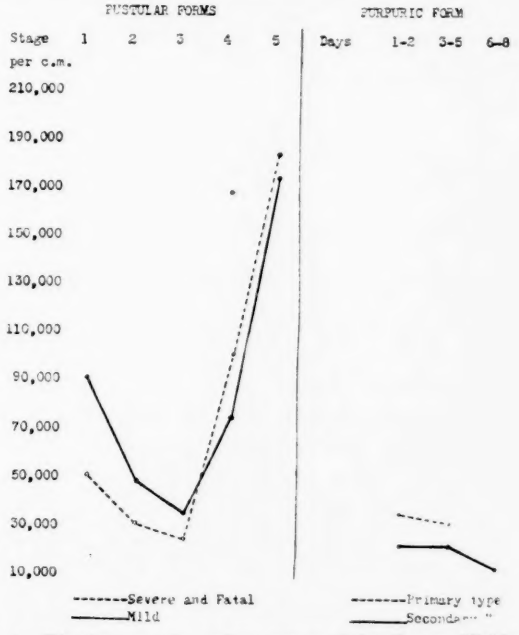

Fig. 1.—Platelet curve in various stages of the disease (Table 2).

In the purpuric form, there is a consistent fall until its termination. The appearance of the modified pocks in the secondary type does not in any way indicate a rise, as in the pustular forms. In the primary type, which shows no visible cutaneous lesions except the deep erythema, petechiae and ecchymoses, an average count is 36,300 per cubic millimeter (highest, 72,000; lowest, 11,000) during the first two days after the development of the initial erythema, and 32,750 per cubic millimeter (highest, 65,000; lowest, 15,500) during the next three days. In the secondary type which runs somewhat a prolonged course and which shows more or less extensive atypical vesiculopustular lesions,

an average count is 23,150 per cubic millimeter (highest, 35,000; lowest, 8,000) during the first two days after the initial rash; 23,750 per cubic millimeter (highest 62,500; lowest, 7,500) during the following three days, and 13,500 per cubic millimeter (highest, 20,000; lowest, 5,000) during the last three days.

The rôle thus played by the platelet count in the differentiation of the purpuric form from the pustular forms of smallpox, and incidentally from eruptive and purpuric diseases, becomes at once of the utmost importance.

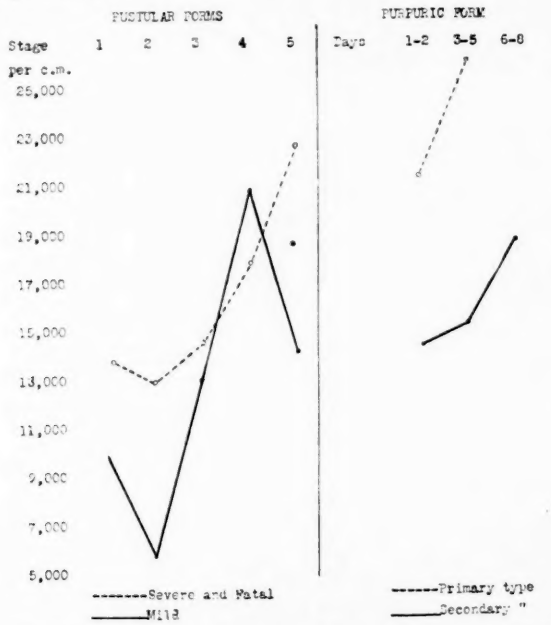

Fig. 2.—Total leukocyte curve in various stages of the disease (Table 2).

THE TOTAL LEUKOCYTE COUNTS (TABLE 2 AND FIG. 2)

Magrath and his co-workers, using the data published by Pick, Courmont and Montagard, Weil and Ferguson, comprised a composite curve obtained from the average of 479 leukocyte determinations in seventy cases of uncomplicated variola vera. The curve thus obtained gives the following formula: relative or absolute hypoleukocytosis during onset and febrile remission; hyperleukocytosis during formative evolution of eruption; relative hypoleukocytosis at height of pustulation and hyperleukocytosis during desiccation. These seventy cases must undoubtedly include the mild as well as the severe and fatal forms of pustular smallpox. The average value thus obtained, therefore, would

not be a reliable index to a particular form that may come under observation.

A leukocytosis (a high leukocyte count) is present, as a rule, during the initial period. In the mild form, an average count of 10,000 per cubic millimeter (highest, 19,000; lowest, 3,000) is obtained. There is, then, a definite decline to an average of 5,883 per cubic millimeter (highest, 9,700; lowest, 3,100) during the maculopapular period which is immediately followed by a sharp rise to an average of 13,200 (highest, 26,000; lowest, 5,500) in the vesicular stage. The highest average is reached in the pustular stage when it is 20,923 per cubic millimeter (highest, 28,000; lowest, 15,900). A decline to an average of 14,630 per cubic millimeter (highest, 33,000; lowest, 7,550) occurs in the desiccation period.

In the severe and fatal forms, an initial leukocytosis averages 13,700 per cubic millimeter (highest, 21,000; lowest, 7,700). It it maintained throughout the course of the disease, an average count being 13,024 per cubic millimeter (highest, 31,340; lowest, 8,000) in the maculopapular period; 14,700 (highest, 33,000; lowest, 6,000) in the vesicular stage, and 17,900 (highest, 31,500; lowest, 13,500) in the pustular stage, reaching its maximum during the period of desiccation, when an average of 22,636 (highest, 37,800; lowest, 11,500) is obtained.

In the purpuric form, likewise, an initial leukocytosis which averages 21,600 per cubic millimeter (highest, 37,000; lowest, 4,400) in the primary type and 14,500 (highest, 31,340; lowest, 9,000) in the secondary type, is maintained throughout the course of the disease. In the majority of cases, a terminal rise is noted, the primary type showing 26,336 (highest, 56,200; lowest, 11,000) during the third, fourth and fifth days after the initial erythema, and the secondary type, 15,431 (highest, 30,600; lowest, 4,600) during the sixth, seventh and eighth days. A leukopenia may be present in this form of smallpox (two cases) as in other severe forms of smallpox.

THE POLYMORPHONUCLEARS (TABLE 2 AND FIG. 3)

The polymorphonuclear neutrophil percentage shows a slight but consistent downward curve through various stages of the disease, regardless of its form or severity. It would seem safe to assert that the higher the polymorphonuclear percentage at the onset or during the initial period, the more grave the prognosis of the subsequent course.

In the mild form, an initial average of 71 per cent (highest, 79; lowest, 60) is followed by a definite drop to 40 per cent (highest, 79; lowest, 28) in the maculopapular stages. There is then a rise to 56.4 per cent and 61.4 per cent, respectively, in the vesicular and pustular stages (vesicular stage, highest, 76; lowest, 39; pustular stage, highest, 69; lowest, 57). This is again followed by a definite fall to 47 per cent (highest, 62; lowest, 17) in the desiccation period.

In the severe and fatal forms, a definitely high average of 83 per cent (highest, 88; lowest, 75) is noted in the initial stage. This is maintained in the subsequent period at 82 per cent (highest, 89; lowest, 75). There is, then, a definite decline during the vesicular stage with an average of 66.7 per cent (highest, 93; lowest, 53) which continues into the period of suppuration with an average of 62.7 per cent (highest, 70; lowest, 54). During the desiccation period an average is 70 per cent (highest, 84; lowest, 41).

In the purpuric form, a rapid drop of the polymorphonuclear neutrophil leukocytes with a continued high total count is consistently present.

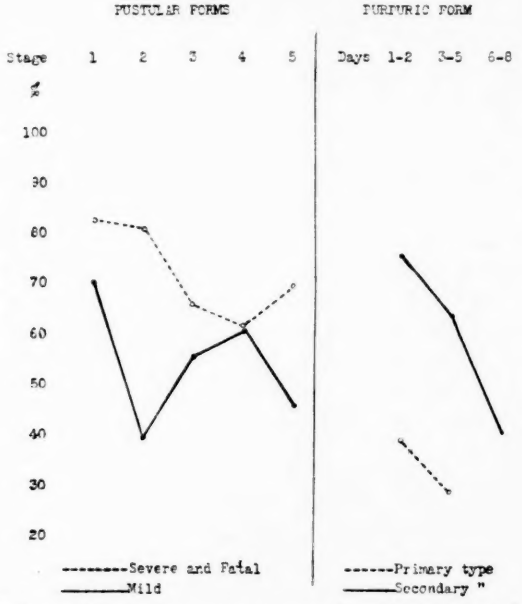

Fig. 3.—Polymorphonuclear percentage curve in various stages of the disease (Table 2).

In the primary type, an average during the first two days is 39 per cent (highest, 73; lowest, 10). During the subsequent three days, it is 28 per cent (highest, 57; lowest, 6). In the secondary type, an average during the first two days is 76 per cent (highest, 88; lowest, 52); during the next three, 64 per cent (highest, 79; lowest, 38), and during the last three days, 40.6 per cent (highest, 73; lowest, 8).

The rapid decrease and probably the ultimate disappearance of the polymorphonuclear leukocytes from the blood is effected by the disintegration of these cells by the toxin in the circulating blood together with the suppression of the leukocytogenesis, and by the stimulation of the lymphocytogenic activity.

RELATION OF TEMPERATURE TO TOTAL LEUKOCYTES AND THE POLYMORPHONUCLEAR NEUTROPHILS (TABLE 2 AND FIG. 4)

Perhaps it would be of interest to dwell briefly on the relation of the temperature to the leukocyte and the differential counts at this time.

In the mild form the temperature is seldom above 102 F. at any period. It registers the highest average of 101.2 F. during the initial period. In the severe and fatal forms the temperature runs considerably higher, often registering 103 and 104. The highest average is reached during the maculopapular period when it is 103.5, with the maximum of 106 and the minimum of 102.2. In the primary type of the purpuric form the temperature is rarely over 101, the highest average being 100.3 during the initial period. In the secondary type of the purpuric form it is 102.6 during the first three days. The total leuko-

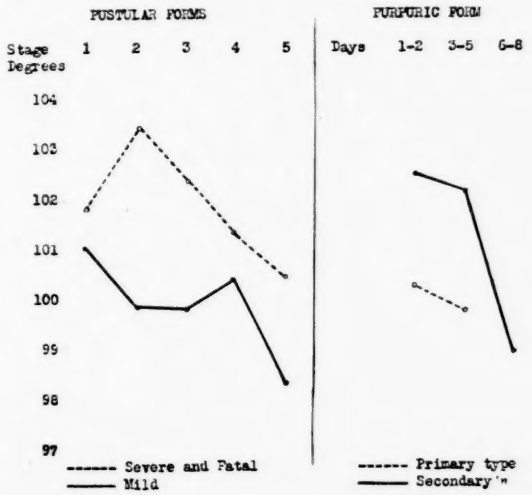

Fig. 4.—Temperature curve in various stages of the disease (Table 2).

cytes show their greatest increase during the later period of the disease, thus showing an entirely diametrical course, while the polymorphonuclear percentage shows its greatest value with the height of the temperature.

It is concluded from these observations that the polymorphonuclear percentage, like the temperature, indicates an immediate reaction of the patient to the infection while the total leukocyte count registers the response of the host to the accumulated insult by that infection.

It is further noted that the temperature in the primary type of the purpuric form is seldom greatly raised. This is probably explained by the presence of an element of shock which must necessarily accompany the diffuse hemorrhages as well as by the overwhelming power of the invading virus, the same as in any other fulminating infection.

THE ERYTHROCYTES

The number of erythrocytes is not appreciably affected in uncomplicated pustular cases. A moderate secondary anemia may develop with the pustulation. The severity of anemia is in direct proportion to the intensity and the extent of the skin lesions, to the amount of toxin absorbed, especially during the pustular stage and to the duration of the disease. It is further influenced by the presence of secondarily invading micro-organisms. Severe protracted cases may show a hemoglobin as low as 25 per cent, and an erythrocyte count of 1,500,000 per cubic millimeter or even less.

In the purpuric form, no appreciable quantitative anemia may be noted. This is particularly true in the primary type in which the course is exceedingly short and abrupt. In the secondary type, as in the severe pustular forms, a high degree of secondary anemia is, as a rule, present.

MORPHOLOGIC CHANGES

The erythrocytes show practically no morphologic or qualitative changes in the ordinary uncomplicated pustular form of smallpox. A secondary anemia, in varying degrees, is present in severe and protracted cases and in those with extensive secondary pyogenic infection, which in the majority of cases is caused by hemolytic streptococci. Low hemoglobin and erythrocyte counts, with a proportionate anisocytosis, polychromatophilia and occasional normoblasts, are the usual findings which persist well into the period of convalescence.

In the purpuric form, the constant presence of an increasing number of pathologic normoblasts, basophilic stippling and polychromatophilia, with a well sustained erythrocyte count and hemoglobin value, is a most striking finding. These regenerative changes of the erythrocytes are encountered even before the clinical evidences of purpura is discovered.

Such forms as plasma cells and "irritation" or "stimulation" forms are constantly found even in the mild form of smallpox. No special significance is attached to their presence. The so-called atypical forms of lymphocytes, which are seldom found in the normal circulating blood, are frequently met with, while the slightly immature forms are also encountered occasionally in severe cases. In the purpuric form, a high percentage of these lymphocytic cells may become a source of added confusion. A leukemia or an acute benign lymphadenosis may naturally be considered as a possibility on the blood smear alone, especially in the presence of a constant high leukocyte count as well as clinical signs of an acute infection. Early cells of the stem cell type and, as a rule, their immediate derivatives are not found.

Such structural changes of the leukocytes as are frequently present in severe sepsis or toxemia are found as a matter of routine. Their frequency depends on the severity of the disease. Even the mild cases

usually show an appreciable degree of these changes. Constantly found are the vacuoles, heavy azure granules, faint neutrophilic granules, clumps of basophilic chromatins in the cytoplasm, and the unilobular and unsegmented nucleus.

Myelocytes and metamyelocytes are often found even in the blood of the milder form. Their number is seldom more than 5 per cent of the total leukocytes, even in the more severe cases. Leukoblastic cells are also met with occasionally. The number of these cells serves in a measure as an index to the response of the bone marrow to the toxemia and therefore to the severity of the disease.

In the blood of the purpuric form certain specific changes are found in the mature leukocytes; namely, a condensation of the nucleus into darker staining homogenous rounded segments which gradually separate into individual nuclear bodies surrounded by more or less residual cytoplasm (Fig. 5). These retrogressive changes are not in any way similar to those due to the disintegration of the leukocytes in the septic blood, or to the faulty technic in making smears. It is easily demonstrated that these fragmentary bodies are of a leukocytic origin by a careful study of the nuclear bodies and the remaining cytoplasm in a properly stained smear. It seems reasonable to assume that they are not of the bone marrow origin but rather formed in the circulating blood or within the diseased tissue by the direct insult of the specific toxin virus on the mature leukocytes. In other words, they represent a true degenerative phenomenon of leukocytes which occurs in certain infectious or toxic processes, the nature of which is not fully understood. Their close resemblance to the normoblasts and to the microlymphocytes should not confuse a careful observer.

At the beginning of this investigation, I was struck with the constant early presence of these fragmentary bodies in the blood of purpuric smallpox. I was soon convinced that similar bodies were consistently absent in the blood of all pustular forms of smallpox. It was therefore provisionally assumed that they were found only in the purpuric form of this disease. This was justified by the subsequent results. Every one of the forty or more cases of purpuric smallpox examined showed these bodies in the blood smears, while none of the more than 200 cases of pustular smallpox showed them at any stage of the disease.

These bodies were discovered during the routine examination of the blood smears and were given their just significance long before I began to consult the literature. Several investigators found the similar bodies in the blood of "hemorrhagic" smallpox and described them. None of them, however, gave their presence a significance which it deserved.

Further search for these bodies was conducted in the blood of exanthematous, septic and toxic disease with or without petechiae and other purpuric states. They were searched in postmortem bloods and in various body fluids. I have found them in the circulating blood of an

acute lymphatic leukemia with extensive petechiae and ecchymoses. I have also found them in the pleural exudates from several cases of acute or subacute pleuritis of an unknown etiology and in the purulent exudate from the peritoneal cavity of a case of chronic tubo-ovarian abscess. Doubtless, they are found in various types of inflammatory exudates.

Magrath [1] and his co-workers mention "the presence of evident degenerative phenomena in the hemorrhagic cases such as . . . .

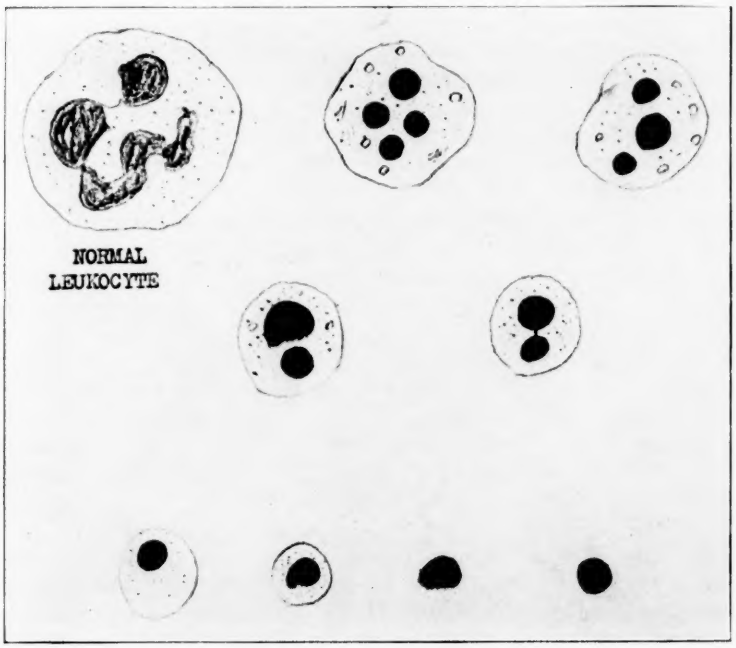

Fig. 5.—Polymorphonuclear neutrophil leukocytes undergoing degenerative changes present in the blood of purpuric smallpox (schematic drawing): segmentation of nucleus into several darkly staining rounded bodies which gradually diminish in number until finally there is a single dark nuclear body or no neutrophilic cytoplasm.

condensation and fragmentation of the nucleus, fragmentation of the whole cells." They do not, however, place any special diagnostic importance on these findings. Ferguson [4] also makes a passing mention of these cells as "the results of degeneration or fragmentation of undoubted polymorphonuclear leukocytes"; he calls misleading and unnecessary the name "small pseudolymphocyte neutrophils" as applied to these cells by Weil, but attaches no specific significance to their pres-

4. Ferguson, A. R.: The Leukocytosis of Variola, J. Path. & Bacteriol. **3**:411, 1902.

ence. Naegeli states that "a complete breaking up of the nucleus into three or four small roundish nuclei can take place during life as a pathologic process. Ehrlich first saw this in a case of hemorrhagic smallpox; and it is seen frequently in fresh exudations."[5] According to Todd[6] these cells are sometimes met with in the blood. He says, "The small neutrophilic cell with a single small round deeply staining nucleus which is sometimes encountered must not be confused with the myelocyte. Such atypical cells probably result from division of polymorphonuclear neutrophils." However, he fails to cite any specific instances or diseases in which they may occur.

In the course of his studies of "the cells in inflammatory exudations" experimentally produced in the peritoneum of guinea-pigs by inoculation of *Bacillus coli* and other pathogenic micro-organisms, Beattie[7] found cells of identical morphology from six to seventy-two hours after such inoculations. He states, "Some of these cells (polymorphonuclear leukocytes) show the nucleus divided up into a number of small, rounded parts. Each of these is uniformly and very darkly stained (twenty-four hours). The polymorphonuclear leukocytes show more of the forms in which the nucleus is broken up into rounded masses stained intensely. Some of these cells have broken up, and darkly stained nuclei are seen free (seventy-two hours)."

It is concluded that condensation and fragmentation of the nucleus in the mature leukocytes, already described and discussed, constitutes one of the important, early diagnostic signs. Demonstrations of these bodies in the blood smear from a given case with prodromal symptoms of an acute infectious disease, with or without erythematous areas, should be considered as a presumptive evidence of purpuric smallpox. In the event of an epidemic, such a demonstration may constitute its positive diagnosis.

OTHER CHANGES

Cells of minor importance, such as the monocytes (large mononucleated leukocytes), the eosinophils and the basophils, show no important variations in their number. A few investigators, notably, Magrath and Ferguson, state that they have observed an increase in the percentage of the large mononuclear leukocytes of the monocyte type. I am inclined to regard at least the majority of these cells as lymphocytes belonging to the slightly early or atypical group. An eosinophilia of from 3 to 10 per cent during the first week and of from 15 to 20 per cent on the eighteenth day is reported by Hoffman who studied a large series of cases in Havana. This is not supported by other men. The

5. Ehrlich, P., and Lazarus, A.: Anemia (translated by H. W. Armit), London, Rebman, 1910, **3**:95.

6. Todd, J. C.: Clinical Diagnosis, Ed. 5, Philadelphia, W. B. Saunders Company, 1924, **3**:321.

7. Beattie, J. M.: The Cells in Inflammatory Exudations: An Experimental Research as to Their Function and Destiny, J. Path. & Bacteriol. **8**:129, 1903.

eosinophilia in this series may therefore be interpreted as due to the prevalence of intestinal parasites among the natives, or possibly to a peculiar tissue reaction of the natives to the smallpox virus.

Various toxic effects on the cytoplasm as are present in the polymorphonuclear leukocytes are noted in these cells.

Thrombopenia seems to have little bearing on the coagulability of the blood in any form of smallpox althugh the coagulation time is definitely hastened during and subsequent to the pustular stage. The bleeding time is appreciably prolonged in purpuric smallpox throughout the course of the disease. This undoubtedly is due to the diminution in the number of platelets coupled with some infectious or toxic process which calls forth the purpuric state and which is not present in the ordinary forms of smallpox.

SUMMARY

An analysis of approximately 250 examinations of the blood in all forms of smallpox reveals the following important points:

1. The blood of the pustular forms of smallpox differs essentially from that of the purpuric form. This is definite and constant and is of value in differential diagnosis.

2. The platelets are greatly diminished in the initial period in all forms of smallpox. In the pustular forms the greatest diminution is reached in the vesicular stage, followed by a rapid rise through the pustular stage into the desiccation period. In the purpuric form the platelet count shows a consistent downward course until death.

3. The total leukocyte count shows at the onset an increase, as a rule, in proportion to the severity of the subsequent course of the disease. In the mild pustular forms a definite leukopenia is present in the maculopapular stages. In the severe and fatal pustular forms a high total count is maintained throughout the course of the disease. Its maximum is reached during the early part of the desiccation period. In the purpuric form an initial hyperleukocytosis is steadily maintained. This is considerably higher in the primary type than in the secondary type. There are few exceptions, both in the pustular forms and in the purpuric form, in which a leukopenia or a normal leukocyte count persists throughout the course of the disease.

4. The polymorphonuclear neutrophil percentage shows a steady downward course in all forms of smallpox except in the desiccation period of the severe and fatal pustular forms. A definite neutropenia of 40 per cent is recorded during the maculopapular stages in the mild form which shows a slight rise during the subsequent stages, declining again to 47 per cent in the desiccation period. A definite polynucleosis is present in the initial and the maculopapular stages in the severe and fatal pustular forms. A decisive neutropenia is obtained in many of the late stages of the purpuric form. The neutrophil fall in this

form is strikingly sudden and spectacular in the presence of a hyperleukocytosis.

5. The temperature and the polymorphonuclears run a parallel course while the total leukocyte count shows a reverse curve in all forms of smallpox.

6. No characteristic changes are noted either in the hemoglobin or in the erythrocyte count. The fact is of significance in the purpuric form in which there are morphologic and qualitative changes of an advanced anemia, usually accompanied by demonstrable, profuse hemorrhages. A definite secondary anemia may develop in severe pustular and protracted secondary purpuric cases, in which a quantitative decrease of the hemoglobin and of the erythrocytes, together with a proportionate morphologic variation, is demonstrated. The decrease may be of such gravity as to require restorative measures.

7. Morphologic changes in the leukocytes and the erythrocytes indicate a severe stimulation of the bone marrow and, in themselves, merely signify various degrees of toxemia or infection. In the blood of the purpuric form, however, there is a series of characteristic metamorphoses in the mature leukocytes which appears to indicate early degenerative changes, specific only in this form of smallpox, and which has served as the only positive laboratory evidence in its diagnosis. This often occurs before any of the clinical signs are evident.

CONCLUSIONS

The blood of smallpox shows characteristic findings which, if properly interpreted, are of definite diagnostic and prognostic value.

1. The earlier the rise of the platelets, the sooner the approach of the desiccation period, prognosticating a shorter course of the disease.

2. A definite leukopenia during the maculopapular stages indicates, as a rule, a mild discrete form. A progressive leukocytosis with an early high polynucleosis predicts a severe form. The higher the values, the more probable the fatal outcome.

3. The early appearance of normoblasts, basophilic stippling and polychromatophila, without evident anemia, is an unfavorable sign. It invariably means the purpuric form of smallpox.

4. Condensation and fragmentation of mature leukocytes are found only in the purpuric form of smallpox. They appear comparatively early in the primary type of purpuric smallpox and are usually accompanied by pathologic normoblasts, basophilic stippling and polychromatophilia, without visible anemia.

5. A rapidly progressive, absolute lymphocytosis is a constant characteristic of purpuric smallpox.

6. Scarlatinal and other exanthems, infectious purpura and toxic rash with petechiae, etc., can be definitely differentiated from the purpuric form of smallpox during its erythematous stage by these blood findings.

GASTRIC SECRETION IN DIABETES MELLITUS

REPORT OF TEN DIABETIC PATIENTS WHO HAD DIARRHEA AND ACHLORHYDRIA *

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During the last two years one of us has encountered ten diabetic patients with either continuous and uncontrollable diarrhea, or attacks of diarrhea. An analysis of the gastric secretion by the fractional method revealed an achlorhydria in each case.

The relationship between the absence of free hydrochloric acid in the gastric contents and a certain type of diarrhea as originally described by Einhorn,[1] who termed it "gastrogenic," is well known. With the advent of the roentgen ray it was possible to study the gastric motility in these cases, and it was noted that the stomach was atonic and emptied rapidly, thus causing a rush of inadequately chymified food into the duodenum. It is the experience of many observers that the diarrhea, in a large percentage of these cases, diminishes or stops with the administration of dilute hydrochloric acid by mouth, even though the administration of the acid does not in any way quantitatively replace the normal amount.

Joslin [2] regards diarrhea in diabetic patients as a serious complication that demands special attention. He also mentions one patient with diarrhea who was very sensitive to insulin. This remarkable sensitivity, even to small doses of insulin, has been present in three of our patients who had diarrhea and emaciation.

In the literature we were unable to find any comment on the gastric secretion in diabetes. Because of the absence of this information and because of the relatively large number of patients who had diarrhea and achlorhydria, we were prompted to make observations on the gastric secretion in all cases of diabetes.

REPORT OF CASES

CASE 1.—*History.*—G. C., aged 33, a restaurant keeper, entered the hospital Sept. 1, 1924, and was discharged September 14. He had been a heavy eater and had drank excessively of alcoholic beverages. He smoked from sixty to seventy cigarets a day. He had undergone the following operations: a cholecystectomy and appendectomy three years before; a gastro-enterostomy two years before and a hemorrhoidectomy three months prior to admission. He stated that he had had

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* From the Buffalo General Hospital.

1. Einhorn, M.: Arch. f. Verdauungskr. **3**:133, 1898.

2. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923, p. 597.

diarrhea ever since the operation two years before, sometimes reaching fifteen movements a day; also, that six months before he developed thirst, frequent urination and a voracious appetite. During that period his weight dropped from 145 to 128 pounds (65.8 to 58.1 Kg.).

Physical Examination.—This showed a rather restless and slightly emaciated man. The skin showed considerable pallor. Marked gingivitis was present. The tonsils were enlarged, and the cervical lymph nodes were palpable. The accessible arteries and veins showed marked thickening and the blood pressure was 90 mm. systolic and 60 diastolic.

Laboratory Findings.—The urine showed a slight trace of albumin; sugar, + + +; no ketones; the sediment was negative. The hemoglobin was 72 per cent; red blood cells, 4,000,000, and white cells, 6,500 per cubic millimeter. The blood urea nitrogen was 16 mg. and the sugar 300 mg. per hundred cubic centimeters. The Wassermann reaction in the blood serum was negative. Fractional analysis of the gastric contents after an Ewald meal showed an achlorhydria in all specimens with a total acidity varying from 22 to 38 degrees. The feces showed a + + benzidin reaction on two occasions; no ova or parasites were found on three examinations. The stools were very large and "soapy" and when stained with sudan III showed an enormous increase in neutral fat.

Fat Excretion (Dr. Anne Viele).—While the patient was receiving a diet of 70 Gm. of carbohydrate, 62 Gm. of protein and 170 Gm. of fat, the weight of the twenty-four hour feces was 882 Gm. The total amount of fat excreted as determined by the Bloor method was 94 Gm., which represented 55 per cent. of the ingested fat.

Course.—The patient was discharged from the hospital on a diet of 70 Gm. of carbohydrate, 62 Gm. of protein and 170 Gm. of fat, which gave 2,058 calories. His urine was free from sugar and his blood sugar during digestion was 200 mg. Fourteen units of insulin was given half an hour before each meal and 2 cc. of dilute hydrochloric acid with each meal. He was followed after his discharge from the hospital for about two months during which time he improved rapidly, remaining free from sugar most of the time but still having from five to ten bowel movements daily. His weight, October 24, was 146 pounds (66.2 Kg.), a gain of 18 pounds (8.2 Kg.). It was learned later that he became careless with regard to his habits of eating and drinking although he continued with the use of insulin most of the time. April 1, 1925, he developed lobar pneumonia and died on the seventh day. Unfortunately, permission for a necropsy was not granted.

This case probably represents a total pancreatitis involving both the external and the internal secretions and also a hyposecretion of the gastric mucosa.

CASE 2.—J. D., aged 55, a housewife, entered the hospital Nov. 2, 1922, and was discharged Jan. 22, 1923. She had had pulmonary tuberculosis of both lungs, chiefly the right, twenty-six years before, for which she had spent considerable time, off and on, at a sanatorium in the mountains. She also stated that she had had attacks of diarrhea lasting for several days for the last year. Two years prior to admission diabetic symptoms began with a rather rapid loss of weight, which dropped from 175 to 100 pounds (79.4 to 45.4 Kg.) on admission.

Physical Examination.—The patient was a thin, poorly nourished woman with dry, warm skin. The right lung showed involvement throughout, with dulness, bronchophony and whispered pectoriloquy in the scapular area only. There were many coarse, crepitant râles throughout. There also were a few râles in the left mammary region. The arteries and the veins were thickened, the former being tortuous. The temperature during her stay in the hospital was usually normal but occasionally went to 99.5 during the afternoon. The pulse was usually around 80. The blood pressure was 120 mm. systolic and 75 diastolic.

Laboratory Findings.—The urinalysis was found to be negative on several examinations with the exception of the presence of sugar and ketones. The blood showed 80 per cent hemoglobin, 8,000 white cells, with 81 per cent of polymorphonuclears. The Wassermann reaction in the blood serum was negative. The sputum on twenty examinations did not show any tubercle bacilli. The blood sugar was found to range between 190 and 290 mg. per hundred cubic centimeters.

Course.—The patient was discharged on a diet of 63 Gm. of carbohydrate, 36 Gm. of protein and 182 Gm. of fat, taking 12½ units of insulin twice a day. The urine remained free from sugar and her blood sugar during digestion was 200 mg. She had been in the hospital for more than two months and despite the fact that her diet had been fairly liberal, and that she had been kept free from sugar most of the time, her weight had dropped to 91 pounds (41.3 Kg.). Some of this, however, was probably loss of fluid. After her discharge, she was seen occasionally for about six months and it was found that she had become very careless about her diet. Nevertheless, her weight increased to 102 pounds (46.3 Kg.). The patient was not seen again until January, 1924, when she was admitted to the hospital in a state of impending coma. After she had made a successful recovery from this, her weight was found to be 99.75 pounds (45.2 Kg.). It was determined that her attacks of diarrhea had been especially annoying and frequent since her discharge a year before. A fractional analysis of the gastric contents showed at that time a complete achlorhydria in all specimens and a variation in the total acidity from 8 to 15 degrees. Dilute hydrochloric acid, 2 cc., was given with the meals and half an hour after. She was discharged from the hospital, January 13, on a diet of 70 Gm. of carbohydrate, 50 Gm. of protein and 150 Gm. of fat, receiving 20 units of insulin half an hour before each meal. She remained on that program for ten months during which time her weight increased up to 159 pounds (72.1 Kg.) and her attacks of diarrhea entirely disappeared. She had, however, recently omitted the hydrochloric acid entirely without any recurrence of diarrhea. July 1, 1925, the gastric contents were again examined by the fractional method with the result that complete achlorhydria was still present. Her weight at this time was 165 pounds (74.8 Kg.).

This case presents several features of interest. First, although irrelevant to the present paper, diabetes followed pulmonary tuberculosis; the tuberculosis, however, was of the chronic fibroid type. Second, the patient did not improve nor gain appreciably in weight during the first year of treatment while receiving 25 units of insulin daily and while having frequent attacks of diarrhea. Later, when the dosage of insulin was increased to 60 units a day and dilute hydrochloric acid was given, the weight increased by 60 pounds (27.2 Kg.) in ten months and the diarrhea disappeared not to recur even though the acid was omitted. As had been expected, the gastric acidity remained the same. It is probable that the eradication of the diarrhea and the increased dosage of insulin improved the patient's nutritional state.

CASE 3.—T. B., aged 40, a business man, was admitted to the hospital, Aug. 30, 1924, and died Nov. 9, 1924. The past history was unimportant except that he had been afflicted with many boils and abscesses ten years before. Diabetic symptoms began six years before and since that time he lost 70 pounds (31.8 Kg.) in weight, his weight on admission being 76 pounds (34.5 Kg.). He had been under treatment in two other hospitals, in one of which he had received insulin. However, he was not faithful to the treatment after his discharge because there did not seem to be any improvement. During the last year he reported that his bowels had been moving from two to six times daily but that during the last few months, the number of movements had increased, sometimes reaching fifteen.

Physical Examination.—The patient was an extremely emaciated man apparently in no discomfort, whose skin was exceedingly dry and wrinkled. The teeth had been extracted and the patient was not wearing the plates that had been made for him. The tongue was dry and smooth. The heart showed a soft systolic murmur at the apex which was not transmitted. The blood pressure was 88 mm. systolic and 72 diastolic. The knee jerks and ankle jerks could not be elicited.

Laboratory Findings.—The urine on admission showed a trace of albumin, and in one specimen a rare hyaline cast. It contained sugar but no ketone bodies. The blood contained 52 per cent of hemoglobin, 3,210,000 red cells and 3,300 white cells, 72 per cent of which were polymorphonuclears. The Wassermann reaction in the blood serum was negative. Fractional analysis of the gastric contents showed no free hydrochloric acid in five specimens collected at twenty-minute intervals. The total acidity, however, increased from 12 to 44 degrees. The basal metabolic rate was plus 1 per cent. The blood sugar was 180 mg. per hundred cubic centimeters.

Pancreatic Enzymes (Dr. J. V. Wadsworth).—The activity of the pancreatic enzymes was studied by the McClure method both when the patient was fasting and after a test meal of 50 cc. of cream into the duodenum. The results are given in Table 1.

All specimens of the duodenal contents were found to be strongly acid and there apparently was rapid emptying of the stomach. Trypsin and steapsin are

TABLE 1.—*Pancreatic Enzymes*

	Trypsin, Mg. of Nonprotein Nitrogen	Steapsin, Cc. of Tenth Normal Sodium Hydroxid	Amylopsin, Mg. of Glucose
Fasting or resting contents	1.3	0.5	3.0
Test meal: 50 cc. cream by mouth			
One-half hour	1.2	0.3	2.0
One hour	9.6	0.2	5.0
Two hours	1.8	0.6	2.0
Normal values	5.0–10.0	2.5–6.0	3.0–10.0

present but reduced from one third to one fourth of the normal values. This reduction is possibly caused by the acidity of the duodenal contents. Amylopsin was present in normal amounts.

Fat Excretion (Dr. Anne Viele).—The fat ingesta in the diet was 150 Gm. during the twenty-four hours. The weight of the feces in twenty-four hours was 235 Gm., which was found to contain 10 Gm. of total fat representing 6.75 per cent of the ingested fat.

Course.—The patient was given a diet of about 1,000 calories and 3 units of insulin before meals. In a few days insulin was increased to four units whereon he developed a severe insulin shock and deep coma. He, however, responded immediately to glucose intravenously. The diet was increased to about 2,000 calories but he would never tolerate more than 4 units of insulin three times a day. The urine remained free from sugar except for an occasional trace in the forenoon specimen. The blood sugar during digestion ranged between 122 and 250 mg. There was no increase in weight. The diarrhea continued without any abatement despite treatment with dilute hydrochloric acid three times a day, bismuth, and at times tincture of opium. October 2, the patient complained of frequency and urgency of urination. The urine was found to contain a large amount of albumin, and pus in the sediment. Several days after that, the patient developed vesical retention and had to be catheterized. October 8, the urologic department made a diagnosis of a "spinal cord bladder" and recommended an indwelling catheter and irrigations twice daily. October 21, the patient developed fever which continued for several days; November 4, an area of redness appeared on the left buttock. November 8, this had developed into an abscess so that it

required drainage. The patient was getting progressively weaker and at times refused to eat. Death occurred, November 9.

Necropsy (Dr. Benjamin Roman).—There were extreme atrophy of the pancreas, which weighed 37 Gm. with considerable fat tissue included, and high grade general emaciation. Diabetes mellitus was diagnosed. The necropsy also revealed: atrophy of the brain with external and internal hydrocephalus and edema of the brain; degeneration of the posterior columns of the cord (tabetic form); brown atrophy of the heart and of the liver; atrophy of the kidneys and of the spleen; large decubitus ulcer and two abscesses in the region of the sacrum (one opened surgically); multiple abscesses of the left kidney; moderate hydrops, ascites, hydrothorax and hydropericardium; edema of the gastro-intestinal mucosa; slight catarrhal cystitis; pressure necrosis in the prostatic urethra; total adhesive pleurisy on the left side with a 10 by 4 cm. osteoma embedded in the thickened pleura, and swelling and contractures of both knee joints.

This patient represents one of those severe cases of diabetes with diarrhea in which the patient can tolerate only very small doses of insulin despite an abundant diet. The hypermotility of the gastro-intestinal tract and unsatisfactory absorption account in some measure for the failure to improve. The stools showed a large amount of undigested material, but, curiously enough, the total fat excreted was only slightly in excess of normal. The external secretion of the pancreas appeared to be present but there was a complete achlorhydria of the gastric secretion. A "spinal bladder" was diagnosed during life and a degeneration of the posterior columns of the cord was found at necropsy. There was no evidence either of syphilis or of pernicious anemia. The patient developed a decubitus ulcer with secondary sepsis which was the immediate cause of death.

DESCRIPTION OF THE TABLES

The cases are divided into three groups. Table 2 contains all cases that showed a complete absence of free hydrochloric acid in all specimens. The cases showing free hydrochloric acid to be absent only in the first few specimens, those in which free hydrochloric acid was present in traces or never exceeded 15 degrees in any specimen are listed in Table 3 under the gastric subacidity group. The patients on whom a normal gastric secretion was found are shown in Table 4.

All patients are listed with relation to the probable duration of the disease beginning with the longest. The severity of the diabetes was crudely estimated by the following symbols which were used in a previous article [3]:

Plus-minus (±) = patients with mild diabetes.
One plus (+) = patients in whom the diabetes was controlled by diet.
Two plus (++) = patients requiring small doses of insulin.
Three plus (+++) = patients requiring large doses of insulin to control the diabetes.

3. Bowen, B. D.; Koenig, E. C., and Viele, A.: A Study of the Lower Extremities in Diabetes as Compared with Nondiabetic States, from the Standpoint of X-Ray Findings, with Particular Reference to the Relationship of Arteriosclerosis and Diabetes, Bull. Buffalo Gen. Hosp. **2**:35 (April) 1924.

COMMENT

A fractional gastric analysis has been made on a series of sixty-nine diabetic patients. These patients have been taken at random, for the most part within the last six months. However, Cases 15, 10, 4 and 1 were encountered before the gastric analyses were reduced to a routine.

TABLE 2.—*Diabetic Patients with Achlorhydria*

Case	Age	Sex*	Probable Duration of Diabetes	Severity of Diabetes	Remarks
1	64	♀	20 years	+++	Chronic nephritis; arterial hypertension; died
2	61	♂	15 years	++	Arteriosclerosis; died from coronary thrombosis
3	64	♀	14 years	+++	Diarrhea; relieved by hydrochloric acid
4	35	♂	12 years	+++	Diarrhea; not relieved by hydrochloric acid
5	55	♀	10 years	+++	Arteriosclerosis; cellulitis of the foot
6	57	♀	9 years	++	Retinitis; diarrhea, relieved by hydrochloric acid
7	69	♀	8 years	++	Gallbladder disease; arteriosclerosis
8	55	♀	7 years	+++	Diarrhea, relieved by hydrochloric acid; died from acute pulmonary tuberculosis
9	39	♂	6 years	+++	Diarrhea, not relieved by hydrochloric acid; extreme emaciation; died
10	55	♀	5 years	++	Diarrhea, relieved by hydrochloric acid
11	48	♀	5 years	++	Arterial hypertension
12	42	♂	3 years	+++	Diarrhea, not relieved by hydrochloric acid; extreme emaciation; died
13	55	♀	3 years	+++	Diarrhea, relieved by hydrochloric acid; fibroid phthisis
14	51	♂	3 years	+++	Precoma
15	62	♀	3 years	++	Diarrhea, relieved by hydrochloric acid
16	33	♂	2 years	+++	Diarrhea, not relieved by hydrochloric acid; steatorrhea; died of lobar pneumonia
17	51	♀	2 years	+++	Achlorhydria on a single specimen; coma
18	53	♂	2 years	+++	Had been obese, had marked loss of weight; advanced pyorrhea
19	46	♂	1 year	+++	Arteriosclerosis
20	59	♀	1 year	+++	Arteriosclerosis

* In this and the succeeding tables, ♂ indicates male; ♀, female.

TABLE 3.—*Diabetic Patients with Gastric Subacidity*

Case	Age	Sex	Probable Duration of Diabetes	Severity of Diabetes	Remarks
21	35	♀	8 years	+	Extreme obesity without loss of weight
22	55	♀	7 years	++	Diabetic "neuritis"
23	58	♀	7 years	+++	Gained 70 pounds (31.8 Kg.) after insulin was given
24	31	♂	6 years	+++	
25	56	♀	5 years	++	Pulmonary tuberculosis; gallbladder disease
26	64	♀	5 years	+	Arteriosclerosis; chronic nephritis
27	56	♀	4 years	+	Arterial hypertension
28	51	♀	3 years	++	Arteriosclerosis
29	34	♀	2 years	+++	Three times in coma
30	58	♀	1 year	++	Premature ventricular contractions
31	36	♀	1 year	++	Cataract which disappeared with insulin
32	25	♂	1 year	++	
33	52	♀	4 months	++	Extreme obesity; chronic myocarditis
34	50	♂	2 months	+++	Carcinoma of head of pancreas; died

On the other hand, gastric analyses have been made on quite a number of earlier patients recently. Because of this it is difficult, if not impossible, to state whether or not these cases which are being reported are representative of other cases had they been chosen in strict succession as they entered the hospital. Also it is more than likely that cases seen in a general hospital are probably more severe and have more compli-

cations than the average of a large number of diabetic patients. In addition, it seems improbable that ten patients with diabetes having diarrhea would ordinarily be encountered in a group of sixty-nine patients. Therefore, it is our impression that this group cannot be judged to be entirely representative, notwithstanding the fact that gastric analyses have been done on all patients who would give us permission, including those who have been admitted to the hospital during the last six months and those who are available from the outpatient department.

The cases showing achlorhydria were 29 per cent of those studied. It can be readily seen by glancing through Table 2, which contains this

TABLE 4.—*Diabetic Patients with Normal Gastric Secretion*

Case	Age	Sex	Probable Duration of Diabetes	Severity of Diabetes	Remarks
35	70	♀	15 years	+	Arteriosclerosis
36	49	♂	12 years	+	Obesity
37	52	♀	8 years	++	Thyroid adenoma
38	64	♀	5 years	++	Marked loss of weight
39	64	♀	5 years	++	Obesity
40	46	♂	5 years	+++	
41	65	♀	4 years	+	Arterial hypertension; gallbladder disease
42	62	♀	4 years	++	Arterial hypertension; gangrene of foot
43	26	♂	4 years	+++	
44	57	♀	3 years	+++	Arterial hypertension; glaucoma
45	56	♂	3 years	++	
46	55	♀	3 years	++	Gallbladder disease
47	48	♀	3 years	+	Arterial hypertension
48	31	♂	2 years	++	
49	70	♂	2 years	++	Arterial hypertension; old hemiplegia
50	63	♀	2 years	++	
51	60	♂	18 months	+	
52	11	♀	14 months	+++	Twice in coma
53	52	♂	1 year	+	
54	56	♂	1 year	+	Gangrene of foot
55	32	♂	1 year	+++	Admitted in coma
56	48	♂	1 year	++	Arteriosclerosis
57	56	♀	1 year	+++	Arteriosclerosis
58	56	♀	1 year	+	Slight arterial hypertension
59	59	♀	1 year	+	Arterial hypertension
60	50	♀	1 year	++	Arthritis deformans
61	58	♀	6 months	+	Obesity
62	53	♀	6 months	+	Slight obesity
63	67	♀	6 months	+	
64	39	♀	5 months	+	Obesity
65	34	♀	3 months	+	Extreme obesity; chronic myocarditis
66	43	♀	3 months	++	
67	75	♀	5 weeks	++	
68	36	♀	4 weeks	++	
69	54	♀	4 weeks*	+	Arterial hypertension; hysteria

* No diabetic history; sugar discovered on admission.

group, that there is no patient having achlorhydria who did not have either severe or long standing diabetes, or both. On the other hand, this statement was by no means found to be reversible, because both the subacidity and the normal groups contain cases of long duration with severe diabetes.

In other words, achlorhydria was not found in any patient who had mild diabetes nor in any patient who had had diabetes for less than a year. However, it was stated that in Case 19 the diabetic symptoms had been present only a year. Notwithstanding this, it is probable,

because of the loss of weight and the rather advanced arteriosclerosis, that the diabetes was of considerably longer duration.

The average duration in the achlorhydria group was 6.6 years; in the subacidity group, 3.6 years; and in the normal group, 2.8 years. In the normal group there are a few cases of quite long duration. Case 37 of eight years' duration was possibly one of thyroid adenoma with glycosuria that later developed into diabetes. Case 39, of five years' duration, was one of obesity. Case 38, of five years' duration, had been mild until the last year. Case 36, of twelve years' duration in a patient with obesity, was apparently mild because there had been little loss of weight and no loss of tolerance during the last four years. Case 35, of fifteen years' duration, was a mild diabetes and a marked senile arteriosclerosis.

Furthermore, it is to be noted that six of the twenty cases with achlorhydria proved fatal while only one of the cases in the gastric subacidity group was fatal, death being due to carcinoma of the pancreas. All the other patients with normal gastric secretion are still living. This, however, may be misleading because, as was stated above, our first observations were only on diabetic patients who had diarrhea and it was in these patients that the majority of deaths occurred. Also, the analyses in the majority of instances have been made so recently that they comprise mostly patients who are doing well. Nevertheless it is significant that 30 per cent of the patients on whom achlorhydria was found died—mostly, as will be noted, from causes possibly secondary to or contributed by rather long standing and uncontrolled diabetes.

Diarrhea was not found in any diabetic patient unless achlorhydria existed and diarrhea occurred in ten out of twenty patients who were found to have achlorhydria. The diarrhea in every case was antedated by the diabetes, usually by a number of years. One of these, Case 16, was one of involvement of both the insular and the acinous portions of the pancreas. In Case 9, the study of the fat excretion before death and the findings of the necropsy would not indicate any involvement of the acini. In Case 12, no studies of the fat excretion were made and permission for a necropsy was not gained. Patient 4, who had had diabetes for twelve years and diarrhea for two years before insulin was started in 1923, had gained from 111 to 143 pounds (50.3 to 64.9 Kg.), during which time he had been taking 40 units of insulin a day and dilute hydrochloric acid with his meals. The diarrhea had not changed perceptibly although there are times when it is absent for several days. Also, in this case, the reduction in the amount of fat in the diet has been tried without any noticeable effect on the number or the character of the movements. Of the ten patients who had diarrhea, four have died; one is not improved, and in six the diarrhea disappeared coincidently with the use of dilute hydrochloric acid. However, the omission

of hydrochloric acid after it had been taken for several months did not effect a return of the diarrhea. Two patients (Cases 17 and 14) who have achlorhydria without diarrhea have been treated with dilute hydrochloric acid for a period of about two months with no improvement in their condition other than would have been expected with insulin alone.

The majority of the patients studied have exceeded the age of 40 years. The average age in the achlorhydria group it 50.7 years; in the normal, 51.1 years, and in the subacidity group, 47.2 years. The youngest patient studied was 11 years and the oldest 75 years; both had normal gastric acidity.

It is unfortunate that we have not tested for the presence of pepsin in every case showing an absence of free hydrochloric acid. Therefore, it is impossible for us to state whether our cases were achlorhydria or true achylia gastrica. However, in several cases only a trace of pepsin was found and in one, Case 10, it was entirely absent. The method of Mett as modified by Nirenstein and Schiff [4] was used, the Mett tubes being prepared by Christiansen's [5] method.

The incidence of achlorhydria in 325 consecutive fractional test meals was found by Hurst [6] to be 10.5 per cent. In a larger series (2,730 cases) Eggleston [7] has reported achlorhydria in 10 per cent. Both call attention to the necessity of using the fractional method of analysis in the diagnosis of true achlorhydria and state that if the single examination were used, the incidence of achlorhydria would be about 9 per cent higher. It is assumed that the cases referred to in these statistics represent both normal and pathologic material. Bennett and Ryle,[8] in a series of fractional gastric analyses on 100 normal subjects, encountered complete absence of free hydrochloric acid in four.

Achlorhydria or achylia gastrica apparently is a condition having a multiple etiology. Its relationship to some diseases such as gallbladder disease, advanced pulmonary tuberculosis, gastric ulcer, hepatic disease, carcinoma of the stomach, or repeated attacks of acute gastritis appears to be secondary. In five cases of carcinoma of the pancreas, one of probable carcinoma and chronic inflammation of the pancreas and in one case in which a definite diagnosis of chronic pancreatitis had been made, Bell [9] has found a complete absence of free hydrochloric acid in

4. Nirenstein and Schiff, in Hawk, P. B.: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1918, pp. 169 and 170.

5. Christiansen, in Hawk (Footnote 4).

6. Hurst, A. F.: Achlorhydria: Its Relation to Pernicious Anemia and Other Diseases, Lancet **1**:111 (Jan. 20) 1923.

7. Eggleston, E. L.: Gastric Secretory Disturbances, Bull. Battle Creek San. and Hosp. Clinic **20**:89 (May) 1925.

8. Bennett, T. I., and Ryle, J. A.: Studies in Gastric Secretion, Guy's Hosp. Rep. **71**:286 (July) 1921.

9. Bell, J. R.: Consecutive Series of 425 Gastric Analyses by the Fractional Method, Guy's Hosp. Rep. **72**:302 (July) 1922.

all specimens. He comments on this finding as probably being more than a mere coincidence. In pernicious anemia, the absence of hydrochloric acid in the gastric secretions apparently precedes the recognizable symptoms of the disease. At this point it is of interest to call attention to the extreme rarity of diabetes mellitus associated with pernicious anemia, as was recently commented on by Adams.[10]

In analyzing the complications and associated diseases of all the cases in the three groups, it does not seem that the recognized causes of achlorhydria are more frequent in the achlorhydria group. In Case 8 the pulmonary tuberculosis was acute and developed after the achlorhydria had been found. In Case 13, fibroid phthisis had probably been present for many years and might have contributed to achlorhydria. It is possible if not probable that gallbladder disease was present in a larger number of patients than was indicated, because we have relied entirely on the characteristic history and physical findings found in that disturbance. In this group, Case 7 was the only one in which such a diagnosis could definitely be made.

According to the observations of McClure, Montague and Mortimer,[11] there does not appear to be any reduction in the enzymic activity of the pancreas in cases of achlorhydria. In a study of the enzymic activity of the pancreatic secretion in a group of sixty-eight diabetic patients, Jones, Castle, Mulholland and Bailey[12] have concluded that there was marked alteration of the external secretory function. They believe that this abnormality is related to the functional or anatomic changes in the acinous tissue of the pancreas and suggest that this diminution may interfere with the proper digestion of protein and fat. They also report that the bile pigment elimination was abnormally high in about 75 per cent of their cases. These findings, in addition to our observations, suggest that possibly in diabetes mellitus there is an abnormality of the entire digestive system.

SUMMARY

1. Fractional gastric analyses have been made on sixty-nine diabetic patients. On critical analysis this group cannot be considered as strictly representative of diabetes as it would be seen in a large group of cases,

10. Adams, S. F.: Three Cases of Pernicious Anemia and Diabetes Mellitus with a Note on the Apparent Ineffectiveness of Insulin in the Presence of a Profound Anemia, M. Clin. N. A. **8**:1163 (Jan.) 1925.

11. McClure, C. W.; Montague, O. C., and Mortimer, E.: Pancreatic Function in the Absence of Free Hydrochloric Acid from the Stomach, Boston M. & S. J. **190**:357 (Feb. 28) 1924.

12. Jones, C. M.; Castle, W. B.; Mulholland, H. B., and Bailey, F. O.: Pancreatic and Hepatic Activity in Diabetes Mellitus: The Alterations with Some Observations on the Etiology of the Disease, Arch. Int. Med. **35**:315 (March 15) 1925.

because of the inclusion of a number of patients who were studied some time before on account of diarrhea, and also because the majority were hospital cases which are possibly more severe than the average.

2. A complete absence of free hydrochloric acid was found in twenty patients, or 29 per cent. Of these, ten had diarrhea while no cases of diarrhea were found in which the patients had free hydrochloric acid. The artificial use of dilute hydrochloric acid did not appear to affect the diarrhea in four patients, three of whom died, one having marked steatorrhea. In the other six patients, the diarrhea stopped coincidently with the use of the acid, but did not reappear when the acid was withdrawn. The patients, however, in all instances took the acid over a period of several months. There was no reappearance of free hydrochloric acid in one case (Case 13) that was subsequently studied.

3. Of the twenty patients who had achlorhydria, the average duration of the diabetes was 6.5 years and diabetes was severe in every case at the time of observation. The duration in the normal group was 2.8 years while the gastric subacidity group held the middle position, with an average of 3.6 years. There was no essential difference in the average ages of the patients in the three groups.

4. In an analysis of the complicating factors in each case, it does not appear that the conditions that are known to produce achlorhydria in nondiabetic subjects are more prevalent in the achlorhydria group.

5. From the results of these observations it seems justifiable to presume that achlorhydria may be the result of long standing or severe diabetes.

HEMOGLOBIN, COLOR INDEX, SATURATION INDEX AND VOLUME INDEX STANDARDS

REDETERMINATIONS BASED ON THE FINDINGS IN ONE HUNDRED AND THIRTY-SEVEN HEALTHY YOUNG MEN *

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The value of color index, volume index and hemoglobin determinations in the differential diagnosis of anemias is well known. But the absence of correct normal standards for the number, volume and hemoglobin content of red cells and the inaccuracy of almost all the clinical hemoglobin methods is a great handicap.

Kern [1] calls attention to the number of widely different hemoglobin figures used as 100 per cent by various authors and instrument makers (e. g., 13.8, 15.0, 15.6, 16.92 and 17.3 Gm. of hemoglobin per hundred cubic centimeters of blood). He emphasizes the importance of knowing the normal amount of hemoglobin per hundred cubic centimeters of blood calculated to a count of 5 million red cells, since this figure forms the basis for the calculation of the color index. Brown and Rowntree [2] state: "The normal standard of hemoglobin is as yet unsettled; this is somewhat surprising in a substance so important."

When our attention was first directed to this problem in the spring of 1919, we, too, were surprised at the scarcity of work on this subject. A study of the available methods of estimating hemoglobin explained everything. These methods were either too inaccurate for research purposes or so technical and time consuming that the labor involved in studying an adequate number of cases was prohibitive. Thus, our first effort was to perfect an accurate, simple method of estimating hemoglobin which would be satisfactory for clinical as well as research use. The method of Osgood and Haskins [3] has made the present study possible.

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1. Kern, R. A.: Problems of Clinical Hemoglobin Estimation, M. Clin. N. Am. **8**:821 (Nov.) 1924.

2. Brown, G. E., and Rowntree, L. G.: The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, Arch. Int. Med. **35**:129 (Jan.) 1925.

3. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107 (Aug.) 1923.

METHODS

Preliminary.—All tests were made on venous blood, drawn by the usual technic. Exactly 10 cc. of blood was quickly and thoroughly mixed with exactly 20 mg.[4] of finely powdered, neutral potassium oxalate to prevent clotting. We strongly recommend the use of oxalated venous blood for all color index and volume index determinations. Our use of such blood guarantees exactly the same concentration of red cells in the portion of blood used for hemoglobin estimation, or for red cell volume determination, as in the portion used for the red cell count. Using separate drops from the ear or finger does not give us any such assurance of uniformity.

Red Cell Counts.—From two to four closely agreeing counts were made on each blood, under my direct supervision, by medical students especially trained for this work. Their results were accepted for this study only after they were able to get duplicate counts varying by less than 100,000 cells per cubic millimeter with regularity. Counting chambers with Levy-Neubauer rulings (tested by the Bureau of Standards) were used. The pipets were carefully recalibrated. Well mixed blood was diluted 1 part in 200 with Toisson's solution and the pipet shaken thoroughly before the counting chamber was filled. After from three to five minutes settling the cells in 100 small squares were counted. The average of the counts on from two to four dilutions of the same blood is the red cell count reported. If the cells were unevenly distributed or if duplicate counts did not agree closely, the results were discarded and all the counts were repeated. We feel that a maximum error of 3 per cent in our reported counts is a conservative estimate.

Cell Volume.—This was determined by centrifugating about 4 cc. of the oxalated blood in a special tube at over 4,500 revolutions per minute until the cell volume remained constant. After an initial period of from twenty to thirty minutes the blood was centrifugated for five minute periods until successive readings showed no change in volume. This is a necessary precaution owing to the great variations in sedimentation time. Most bloods will be completely sedimented in one-half hour at this speed, but a few require more than one hour. The centrifuge tube that we used was prepared by sealing the tip of a 10 cc. Mohr pipet (graduated to the tip) and cutting it off a little above the 6 mark (capacity, 4 cc.). It was carefully recalibrated. Fitted with corks as shown in figure 1, it is well supported by the ordinary centrifuge tube holder. Such a narrow tube permits of accurate readings on 3 or 4 cc. of blood. However, if 10 cc. of blood is available, satisfactory

4. For ordinary clinical purposes 1 drop of 30 per cent potassium oxalate solution is satisfactory.

estimations can be made in an ordinary graduated centrifuge tube. This must, of course, be recalibrated. The possible objection to our manner of using potassium oxalate is answered and other methods of cell volume determination are discussed elsewhere in this paper.

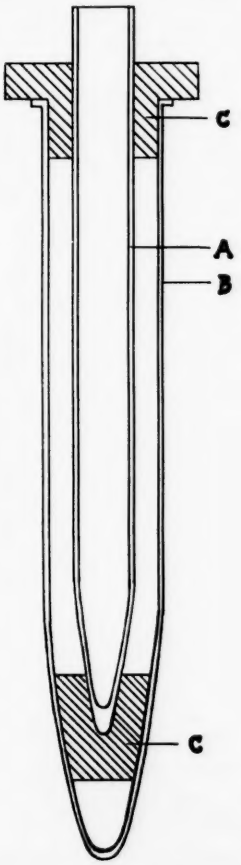

Fig. 1.—Tube used in centrifugating; *A*, tube; *B*, holder; *C*, corks to act as supports.

Hemoglobin Estimations.—Hemoglobin was estimated by our own method.[3] The hemoglobin was converted into acid hematin by first laking exactly 1 cc.[5] of well mixed oxalated blood with about 45 cc. of distilled water in a 100 cc. flask, and then treating with 50 cc. of one-

5. As little as 0.05 cc. may be taken, if 2.45 cc. of water and 2.5 cc. of acid are used. Greater accuracy is insured by our larger quantities.

fifth normal hydrochloric acid (18 cc. of chemically pure acid diluted to 1 liter is satisfactory). After diluting to the mark and mixing, the maximum acid hematin color was developed by heating a test tube full in a water bath kept at about 55 C. for seven minutes (or the acid hematin may stand twenty-four hours at room temperature in the dark). The cooled solution was then compared with our permanent standard (set at 15 mm.) in a Kober colorimeter [6] by artificial light. The temperature of the standard was taken with a reliable thermometer after each reading. The percentage of hemoglobin (100 per cent by our method means that the blood contains 13.8 Gm. of hemoglobin per hundred cubic centimeters and has an oxygen capacity of 18.5 cc.) was read from our

TABLE 1.—*Comparison of Estimations of Hemoglobin by Osgood and Haskins' Method and by Van Slyke's Method*

Blood No.	Percentage of Hemoglobin	
	New Method	Van Slyke's Method*
1	29.7	30.6
2	37.0	36.8
3	43.7	42.9
4	49.7	49.0
5	56.0	56.0
6	61.0	61.3
7	65.7	66.0
8	72.3	74.0
9	80.4	79.8
10	90.8	91.9
11	96.2	96.7
12	100.5	100.0
13	104.8	104.6
14	117.3	116.8
15	123.2	122.6
16	131.3	132.2

* We found it necessary to take the mean of several Van Slyke estimations in order to keep the probable error below 1 per cent. The results by our method given above are also the mean of several determinations.

special table in the column under the temperature of the standard solution and opposite the colorimeter reading. The results reported were based on the average of four such readings, but were calculated to grams of hemoglobin per hundred cubic centimeters. Certified pipets and flasks were used for all measurements.

The accuracy of our method was proved by comparison with Van Slyke's [7] latest method (the accepted standard research method). Table 1 shows that in only one case is the difference as great as 1 per cent between the result by our method and the average of several estimations by the

6. The colorimeter and lamp were kept in fixed positions, so that the colorimeter was always in proper adjustment for the estimation. The use of daylight involves frequent resetting of the colorimeter.

7. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, J. Biol. Chem. **49**:1 (Nov.) 1921.

Van Slyke technic. The maximum error, therefore, in any one of our hemoglobin estimations is certainly not over 2 per cent.

We wish to emphasize the fact that all the methods we have used, while of research accuracy, are also clinically practical. None is too time consuming or too difficult for any careful technician. Furthermore, these methods do not require extra apparatus not found in every well equipped clinical laboratory.

SUBJECTS EXAMINED

One hundred and thirty-seven male medical students between the ages of 19 and 30 were studied. The age, height, weight and nationality of each was recorded. As no use has been made of the height and weight figures in this paper they are omitted. The majority were American born of American parents. Most of the others were American born of foreign born parents. Aside from American, the nationalities chiefly represented were English, Scotch, Scandinavian and German. These subjects, we believe, furnish a fair cross-section of the population of this sex and age in the Pacific Northwest. There were not enough men of any one nationality to justify an analysis on this basis, so the nationalities are not reported.

Each man considered himself perfectly healthy at the time the blood was drawn, and each had had a medical examination during the school year, so that it is safe to say that they were in good health when examined.

Most of the bloods were drawn between two and three in the afternoon. However, no particular effort was made to take bloods always at the same time of day, as this is not done in clinical practice and we wished to determine the full range of normal variation.

About one-half the examinations were made in the spring. The rest were distributed about equally between the fall and winter months. No examinations were made in the summer. We do not report the dates since an analysis of our results showed no significant seasonal variations.

THE RED CELL COUNT IN NORMAL MALES

The figures for average normal counts (5 million for men and 4.5 million for women) were adopted a long time ago, and have been quoted from one text to another without proper confirmation. Few physicians are aware that these figures were based on examination of a small number of bloods. Vierord (1852) and Welcher (1854), each of whom examined the blood of only two persons, are responsible for these figures (according to Bie and Möller [8]).

8. Bie, V., and Möller, P.: Undersogelser af normale Menneskers Blod, Ugesk. f. Læger, 1913, pp. 749, 817 and 878; Le Sang Humain Normal, Arch. d. mal. du cœur **15**:177 (April) 1922.

TABLE 2.—*Blood Findings in One Hundred and Thirty-seven Normal Young Men*

Subject	Age	Red Cell Count, Millions per Cmm.	Hemoglobin, Grams per 100 Cc.	Hemoglobin per 100 Cc. per 5 Million Cells	Color Index	Volume of Cells per 100 Cc.	Volume of Cells per 100 Cc. per 5 Million	Volume Index	Saturation Index
1	21	5.73	14.12	12.32	0.84	43.38	37.86	0.92	0.91
2	25	5.61	14.11	12.57	0.85	40.10	35.75	0.87	0.98
3	24	5.83	14.70	12.60	0.86	42.97	36.85	0.90	0.98
4	29	6.24	16.09	12.89	0.88	49.47	39.65	0.97	0.91
5	29	5.95	15.35	12.90	0.88	44.25	37.18	0.91	0.97
6	22	6.12	16.01	13.06	0.89	45.86	37.41	0.91	0.97
7	25	5.72	14.96	13.06	0.89	39 40	34.56	0.84	1.05
8	27	5.90	15.79	13.08	0.89	45.33	38.42	0.94	0.96
9	24	5.62	14.77	13.14	0.89	45.00	40.03	0.98	0.91
10	25	6.14	16.15	13.15	0.89	.....	.....	....	....
11	19	6.27	16.53	13.18	0.90	45 07	35.94	0.88	1.02
12	22	5.65	15.08	13.35	0.91	.....	.....	....	....
13	21	6.23	16.64	13.36	0.91	50.13	40.24	0.98	0.92
14	23	5.96	16.03	13.44	0.91	45.32	38.02	0.93	0.99
15	23	5.91	15.88	13.44	0.91	44.74	37.85	0.92	0.99
16	20	5.80	15.59	13.44	0.91	45.82	39.50	0.96	0.95
17	22	5.61	15.08	13.46	0.91	45.10	40.26	0.98	0.94
18	25	5.98	16.17	13.52	0.92	43.75	36.58	0.89	1.03
19	24	5.68	15.39	13.54	0.92	.....	.....	....	....
20	26	5.52	14.98	13.56	0.92	42.05	38.09	0.93	0.99
21	24	5.33	14.60	13.70	0.93	44.39	41.64	1.02	0.91
22	21	5.10	14.01	13.73	0.93	41.43	40.62	0.99	0.94
23	25	5.32	14.63	13.75	0.93	44.05	41.40	1.01	0.92
24	26	6.17	17.37	13.76	0.93	.....	.....	....	....
25	26	5.72	15.77	13.78	0.94	43.41	37.95	0.93	1.02
26	24	5.81	16.02	13.79	0.94	47.56	40.93	1.00	0.94
27	24	5.72	15.87	13.87	0.94	.....	.....	....	....
28	30	5.18	14.38	13.88	0.94	41.84	40.39	0.98	0.96
29	25	5.10	14.18	13.90	0.94	.....	.....	....	....
30	22	5.42	15.10	13.93	0.95	44.58	41.13	1.00	0.95
31	27	4.82	13.44	13.94	0.95	.....	.....	....	....
32	26	5.22	14.55	13.96	0.95	38.51	36.88	0.90	1.06
33	25	5.54	15.47	13.96	0.95	42.50	38.37	0.94	1.01
34	24	5.45	15.25	13.99	0.95	44.98	41.27	1.01	0.94
35	27	5.00	13.99	13.99	0.95	41.43	41.43	1.01	0.94
36	24	5.00	14.01	14.01	0.95	.....	.....	....	....
37	29	6.29	17.64	14.02	0.95	48.29	38.38	0.94	1.01
38	22	6.40	18.00	14.06	0.95	50.00	39.05	0.95	1.00
39	23	5.68	15.25	14.06	0.95	44.74	41.24	1.01	0.95
40	23	5.22	14.68	14.06	0.95	46.38	44.43	1.08	0.90
41	22	5.69	16.02	14.08	0.96	48.91	42.98	1.05	0.91
42	28	4.82	13.61	14.11	0.96	41.18	42.71	1.04	0.92
43	23	5.37	15.17	14.12	0.96	.....	.....	....	....
44	30	5.84	16.52	14.14	0.96	48.97	41.93	1.02	0.94
45	25	5.24	14.82	14.14	0.96	41.98	40.05	0.98	0.99
46	22	5.63	15.94	14.16	0.96	47.00	41.74	1.02	0.94
47	22	5.87	16.64	14.17	0.96	46.00	39.18	0.96	1.00
48	22	5.40	15.32	14.18	0.96	45.61	42.23	1.03	0.94
49	24	5.24	14.89	14.21	0.97	45.13	43.06	1.05	0.92
50	22	5.09	14.48	14.22	0.97	.....	.....	....	....
51	25	5.60	15.92	14.22	0.97	46.15	41.20	1.00	0.97
52	28	5.68	16.17	14.24	0.97	47.32	41.60	1.02	0.95
53	27	4.97	14.13	14.25	0.97	.....	.....	....	....
54	20	5.69	16.24	14.27	0.97	49.87	43.82	1.07	0.91
55	23	5.14	14.67	14.27	0.97	.....	.....	....	....
56	21	5.88	16.79	14.28	0.97	48.00	40.82	1.00	0.97
57	24	5.33	15.26	14.32	0.97	.....	.....	....	....
58	22	5.33	15.30	14.33	0.97	44.16	42.31	1.03	0.94
59	23	5.22	14.96	14.33	0.97	.....	.....	....	....
60	25	6.36	18.23	14.33	0.97	45.13	35.48	0.87	1.13
61	24	5.26	15.10	14.36	0.96	43.59	41.45	1.01	0.97
62	24	5.07	14.57	14.36	0.98	.....	.....	....	....
63	25	5.39	15.55	14.41	0.98	.....	.....	....	....
64	27	5.28	15.24	14.43	0.98	.....	.....	....	....
65	24	5.08	14.67	14.44	0.98	42.34	41.67	1.02	0.97
66	24	5.52	16.01	14.50	0.98	45.05	43.52	1.06	0.93
67	28	5.47	15.89	14.52	0.99	46.41	42.43	1.03	0.95
68	20	5.20	15.10	14.52	0.99	45.70	43.94	1.07	0.92
69	27	5.15	14.99	14.55	0.99	.....	.....	....	....
70	26	5.62	16.37	14.56	0.99	47.93	42.65	1.04	0.95

TABLE 2.—*Blood Findings in One Hundred and Thirty-Seven Normal Young Men (Continued)*

Subject	Age	Red Cell Count, Millions per Cmm.	Hemoglobin, Grams per 100 Cc.	Hemoglobin per 100 Cc. per 5 Million Cells	Color Index	Volume of Cells per 100 Cc.	Volume of Cells per 100 Cc. per 5 Million	Volume Index	Saturation Index
71	25	5.58	16.26	14.57	0.99	.....	.....	....	....
72	24	5.52	16.10	14.59	0.99	45.50	41.31	1.01	0.98
73	27	5.43	15.85	14.60	0.99	46.61	42.91	1.05	0.95
74	21	5.02	14.75	14.69	1.00	36.61	36.17	0.88	1.13
75	28	5.21	15.15	14.71	1.00	44.25	42.96	1.05	0.96
76	23	5.22	15.42	14.75	1.00	40.00	38.31	0.94	1.06
77	25	5.14	15.16	14.75	1.00	43.42	42.24	1.03	0.97
78	23	5.24	15.51	14.80	1.01	45.33	43.25	1.05	0.95
79	21	5.27	15.60	14.80	1.01	41.47	39.35	0.96	1.05
80	25	5.50	16.28	14.80	1.01	40.00	36.36	0.89	1.14
81	23	5.64	16.62	14.84	1.01	43.67	39.90	0.98	1.03
82	26	5.30	15.75	14.85	1.01	45.95	43.35	1.06	0.95
83	22	4.93	14.68	14.89	1.01	.....	.....	....	....
84	24	5.44	16.20	14.89	1.01	48.49	44.56	1.09	0.93
85	24	5.50	16.38	14.89	1.01	47.38	43.08	1.05	0.96
86	24	4.88	14.55	14.90	1.01	.....	.....	....	....
87	22	5.15	15.36	14.91	1.01	46.13	44.79	1.09	0.93
88	27	4.78	14.26	14.92	1.01	.....	.....	....	....
89	23	4.94	14.68	14.92	1.01	41.67	42.17	1.03	0.98
90	27	5.57	16.63	14.93	1.01	48.93	43.55	1.06	0.95
91	21	5.21	15.55	14.93	1.01	.....	.....	....	....
92	27	4.94	14.77	14.95	1.02	45.57	46.13	1.12	0.90
93	22	6.01	17.98	14.96	1.02	45.71	38.03	0.93	1.10
94	21	5.26	15.77	14.99	1.02	45.96	43.68	1.06	0.96
95	24	5.53	16.71	15.11	1.03	.....	.....	....	....
96	22	5.75	17.39	15.12	1.03	45.26	39.44	0.96	1.07
97	24	5.49	16.62	15.13	1.03	46.50	42.35	1.03	1.00
98	28	5.46	16.53	15.14	1.03	46.69	42.75	1.04	0.99
99	30	5.99	18.18	15.17	1.03	47.48	39.63	0.97	1.07
100	27	5.16	15.66	15.18	1.03	.....	.....	....	....
101	27	5.99	18.63	15.20	1.04	47.79	39.90	0.97	1.08
102	23	5.16	15.83	15.24	1.04	.....	.....	....	....
103	24	5.08	15.50	15.25	1.04	.....	.....	....	....
104	25	5.17	15.79	15.27	1.04	36.09	34.91	0.86	1.21
105	25	5.53	16.93	15.31	1.04	46.68	42.21	1.03	1.01
106	29	5.24	16.09	15.35	1.04	.....	.....	....	....
107	25	5.10	15.66	15.35	1.04	.....	.....	....	....
108	24	5.28	16.25	15.39	1.05	45.20	42.81	1.04	1.01
109	29	5.74	17.65	15.39	1.05	49.17	42.83	1.04	1.01
110	27	5.54	17.07	15.41	1.05	46.78	42.22	1.03	1.02
111	29	4.99	15.46	15.49	1.05	43.00	43.09	1.05	1.00
112	22	5.71	17.72	15.52	1.05	48.16	42.17	1.03	1.02
113	23	5.88	18.33	15.59	1.06	48.10	40.90	1.00	1.06
114	23	5.68	17.75	15.62	1.06	47.01	41.38	1.01	1.05
115	24	5.08	15.87	15.62	1.06	43.38	42.69	1.04	1.02
116	22	5.14	16.06	15.63	1.06	40.52	39.41	0.96	1.11
117	20	5.60	17.53	15.65	1.06	47.00	41.96	1.02	1.04
118	24	5.16	16.22	15.71	1.07	44.97	43.59	1.06	1.01
119	23	4.46	14.04	15.72	1.07	40.82	45.72	1.12	0.96
120	25	4.70	14.80	15.77	1.07	41.28	43.92	1.07	1.00
121	28	4.81	15.36	15.96	1.08	.....	.....	....	....
122	28	4.83	15.44	15.99	1.09	.....	.....	....	....
123	25	4.84	15.49	16.00	1.09	.....	.....	....	....
124	22	5.12	16.50	16.09	1.09	.....	.....	....	....
125	27	4.91	15.84	16.11	1.11	.....	.....	....	....
126	22	5.31	17.40	16.38	1.12	40.00	37.67	0.92	1.21
127	25	4.78	15.66	16.38	1.12	40.57	41.91	1.02	1.09
128	25	4.73	15.55	16.44	1.12	.....	.....	....	....
129	26	4.92	16.23	16.49	1.12	.....	.....	....	....
130	23	5.74	19.03	16.58	1.13	51.87	45.19	1.10	1.02
131	24	5.31	17.66	16.63	1.13	.....	.....	....	....
132	28	4.70	15.65	16.65	1.13	.....	.....	....	....
133	24	4.49	14.96	16.65	1.13	.....	.....	....	....
134	27	4.85	16.26	16.75	1.14	.....	.....	....	....
135	25	4.57	15.97	17.47	1.19	.....	.....	....	....
136	26	4.41	15.66	17.76	1.21	.....	.....	....	....
137	27	4.83	17.25	17.85	1.21	.....	.....	....	....
Average....		5.39	15.76	14.66	1.00	44.84	40.80	1.00	1.00

A survey of the literature to date (September, 1925) shows that reasonably accurate red cell counts have been reported for only thirty-one normal males between the ages of 19 and 30 (the age limits for our work reported in this paper) distributed as follows:

Bierring[9]: 4 men, averaging 5.05 million.
Gram and Norgaard[10]: 7 men, averaging 5.40 million.
Haden[11]: 20 men, averaging 5.08 million.
Total: 31 men, averaging 5.15 million.

These are the only counts that can properly be compared with our own. The average count on our 137 men was 5.39 million.[12] Our counts ranged from 4.4 to 6.4 million, while in the thirty-one counts cited above the range was from 4.52 to 5.91 million.

Aside from the work reported above, presumably accurate counts on 153 men are given in the literature, without any statement as to ages. They are distributed as follows:

Capps[13]: 4 men, averaging 5.15 million.
Bock[14]: 4 men, averaging 4.95 million.
Bie and Möller[8]: 10 men, averaging 5.53 million.
Larrabee[15]: 13 men, averaging 5.33 million.
Bing[16]: 19 men, averaging 5.50 million.
Gram[17]: 32 men, averaging 5.37 million.
Ten other authors[18]: 71 men, averaging 5.39 million.
Total[19]: 153 men, averaging 5.38 million.

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9. Bierring, K.: Svingninger i Erythrocyttallet hos normale Mennesker, Ugesk. f. Læger **82**:1445 (Nov. 18) 1920.

10. Gram, H. C., and Norgaard, A.: Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects, Arch. Int. Med. **31**:164 (Feb.) 1923.

11. Haden, R. L.: The Normal Hemoglobin Standard, J. A. M. A. **79**:1496 (Oct. 28) 1922; Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:766 (May) 1923.

12. Reference should be made to table 2 for our detailed results.

13. Capps, J. A.: A Study of the Volume Index, J. M. Res. **10**:367 (Dec.) 1903.

14. Bock, A. V.: The Constancy of the Volume of the Blood Plasma, Arch. Int. Med. **27**:83 (Jan.) 1921.

15. Larrabee, R. C.: The Volume Index of the Red Corpuscles, J. M. Res. **24**:15 (Jan.) 1911.

16. Bing, H. I.: On the Number of Red Blood Corpuscles at Different Ages and Under Different Circumstances, Proc. Ninth Northern Congress Int. Med., Acta med. Scandinav. **53**:833, 1921.

17. Gram, H. C.: Om det normale Erythrocyttale og den normal Hemoglobinmaengde i Veneblod, Ugesk. f. Læger **82**:1543 (Dec. 9) 1920; On the Standardization of Hemoglobinometers and Its Importance for Index Calculation, Acta med. Scandinav. **57**:27 (Nov.) 1922.

18. Writers quoted by Bie and Möller (Footnote 8).

19. The average of 4.92 million obtained by E. Meyer and E. E. Butterfield (The Color Index of the Red Corpuscles, Arch. Int. Med. **14**:94 [July] 1914) on seven men (ages not reported) is not included because they used defibrinated blood. It is obviously impossible to defibrinate blood without changing the red cell count.

The close agreement of this general average with our average (5.39 million) may be accounted for if, as is probable, these investigators examined the blood of college students (men of the same age limits as ours). The counts on the 153 men ranged from 4.2 to 6.39 million (ours ranged from 4.4 to 6.4 million).

It is fully as important, however, to know the range of the most frequently occurring normal red cell counts as to know the extreme limits. Frequency figure 2 shows the distribution of our 137 counts. From it we see that counts at any point between 4.9 and 5.9 million are common, while about 90 per cent of them fall between 4.7 and 6.1 million cells.

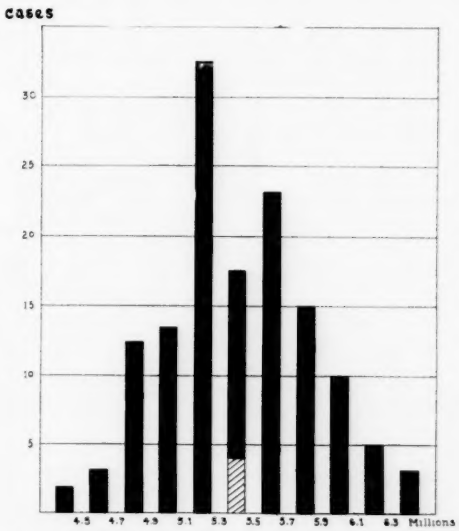

Fig. 2.—Red cell counts in one hundred and thirty-seven healthy young men.

The tendency to a double peak in the chart probably is not significant. If a large enough number of men were examined the most frequently occurring, as well as the average, figure would undoubtedly be about 5.4 million. The average is indicated in the chart (similarly also in figures 3 to 7) by a column having oblique lines in the lower portion. It will also be noticed that counts between 4.4 and 4.7 million and between 6.1 and 6.4 million do occur occasionally in normal men. Yet textbooks still state that a red cell count of 6 million or more justifies a diagnosis of polycythemia.

HEMOGLOBIN CONTENT OF THE BLOOD IN NORMAL MALES

The literature on normal hemoglobin standards is difficult to summarize because so many different methods of hemoglobin estimation have

been used, few of which are sufficiently accurate for research purposes. Thus, we have found in the literature reliable hemoglobin estimations reported for only seventy males between 19 and 30 years of age. The average grams of hemoglobin per hundred cubic centimeters of blood for each group of cases follows:

Brown [20] and Rowntree [2] (Palmer's method, checked by Osgood-Haskins' method): 7 men, averaging 16.27 Gm.
Gram and Norgaard [10] (Autenrieth-Konigsburger colorimeter method): 7 men, averaging 14.83 Gm.
Haden [11] (Van Slyke's method): 20 men, averaging 15.83 Gm.
Williamson [21] (spectrophotometer): 36 men, averaging 16.80 Gm.
Total: 70 men, averaging 16.27 Gm.

This average is not widely different from our average of 15.76 Gm. for 137 men. If we figure in our results, the average for the total 207 men is 15.93 Gm. This figure is much higher than the 13.8 Gm. quoted in most texts. The wide variations in the averages reported by different authors, as shown in the preceding paragraph, is probably due to the small number of men examined. The extremes in thirty-four [22] of the seventy examinations are 13.30 and 19.46 Gm. Our extremes on 137 men are 13.44 and 19.03 Gm.

Beside the foregoing cases (which are the only ones comparable to our own) we have found the following reports of accurate estimations on thirteen adult males, the ages not being given:

Bock [14] (Van Slykes method): 3 men, averaging 17.0 Gm.
Lundsgaard [23] (Palmer's method): 10 men, averaging 14.7 Gm.
Total: 13 men, averaging 15.23 Gm.

For the sake of completeness we include the following reports of examinations of 132 men by obsolete or unsatisfactorily standardized methods:

Bie and Möller [8] (Meisling colorimeter): 10 men, averaging 14.80 Gm.
Haldane [24] (Haldane oxygen capacity method) [25]: 12 men, averaging 13.80 Gm.
Haldane and Smith [26] (Haldane's method): 12 men, averaging 13.80 Gm.
Bing [16] (Sahli method): 19 men, averaging 15.46 Gm.

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20. Brown, G. E.: Personal communication to the author on age and sex.

21. Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505 (Oct.) 1916.

22. Williamson (footnote 21) did not report his extremes.

23. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, J. Biol. Chem. **33**:133 (Jan.) 1918.

24. Haldane, J.: The Colorimetric Determination of Hemoglobin, J. Physiol. **26**:497 (June) 1901.

25. All of Leichtenstern's and six of Haldane's patients were between 19 and 30 years of age. No statement is made about age by the other authors.

26. Haldane, J., and Smith, J. L.: The Mass and Oxygen Capacity of the Blood in Man, J. Physiol. **25**:331 (Aug.) 1900.

Leichtenstern [27] (spectrophotometer [28]) : 22 men, averaging 14.40 Gm.[29]
De Jong [29] (Sahli method) : 25 men, averaging 12.63 Gm.
Gram [17] (Autenrieth Hellige colorimeter) : 32 men, averaging 13.66 Gm.
Total: 132 men, averaging 13.96 Gm.

Results as low as 11.7 Gm. and as high as 17 Gm. are included in the foregoing.

The 13.8 Gm. figure given in many texts is based on the few estimations reported by Haldane,[24] made by a method that is now obsolete. He reported no red cell counts, so that even supposing his hemoglobin

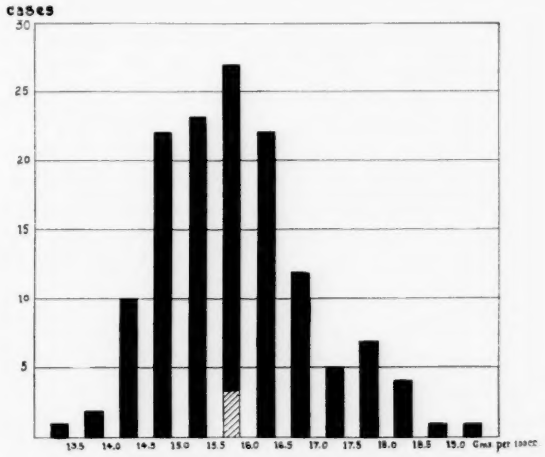

Fig. 3.—Total hemoglobin in one hundred and thirty-seven men.

determinations were correct, the use of 13.8 Gm. of hemoglobin per hundred cubic centimeters as 100 per cent in computing color indexes has never been justified.

As the hemoglobin estimations reported by Laache,[30] Capps,[13] Meyer and Butterfield,[19] Rossdale [31] and Emerson [32] were too inaccurate to be of value, they are omitted.

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27. Leichtenstern, O.: Untersuchungen über den Haemoglobingehalt des Blutes in gesunden und kranken Zuständen, Lepizig, 1878.

28. Sahli (Diagnostic Methods, 1911, p. 743) is authority for the basis of calculation of this figure from Leichtenstern's data.

29. De Jong, J. J.: Le Taux de le Hemoglobine du Sang et le Volume des Globules Rouges par Rapport a la Signification de la Valeure Globulaire, Presse méd. **32**:789 (Oct. 1) 1924.

30. Laache, S.: Die Anämie, Christiania, 1883.

31. Rossdale, G.: Observations with the Hematocrit Volume-Color Index, Quart. J. Med. **16**:245 (April) 1923.

32. Emerson, C. P.: Clinical Diagnosis, ed. 5, Philadelphia, J. B. Lippincott Company, 1921, p. 44.

Our average of 15.76 Gm. of hemoglobin per hundred cubic centimeters of blood is also the most frequently occurring figure (fig. 3). Over 90 per cent of the estimations are between 14 and 18 Gm.

COLOR INDEX

The essentials for a color index determination that will be of value in diagnosis are:

1. An accurate red cell count on the patient's blood.
2. An accurate hemoglobin estimation on the same blood.
3. A normal standard for comparison. This standard is the average number of grams of hemoglobin per hundred cubic centimeters of blood calculated to a count of 5 million red cells per cubic millimeter in the average healthy person of the same age and sex. We suggest the term *hemoglobin coefficient* to replace the cumbersome expression "the number of grams of hemoglobin per hundred cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeter." We use it hereafter with this meaning. The color index is calculated by dividing the percentage of hemoglobin by the percentage of red cells. For this calculation the normal hemoglobin coefficient (for the patient's age and sex) is considered as 100 per cent, and a red cell count of 5 million is considered as 100 per cent.

Previous to our work the normal hemoglobin coefficient has never been satisfactorily determined for any sex or age group. Enough data has been accumulated, however, to show that it probably does vary with age and sex, and that neither 13.8 Gm. nor 16.92 Gm. (100 per cent hemoglobin equivalents on the reading scales of two commonly used hemoglobinometers) is anywhere near the correct figure for adult males. Therefore it is necessary to convert all hemoglobin estimations into terms of grams per hundred cubic centimeters before calculating color indexes, and it would be desirable to have all hemoglobinometers standardized to read in grams per hundred cubic centimeters. Until this has been brought about each clinician should find out the number of grams of hemoglobin equivalent to 100 per cent on his hemoglobinometer, and then convert his results into grams per hundred cubic centimeters.

Many physicians do not seem to be aware that the most commonly used methods of hemoglobin estimation are not sufficiently accurate for color index work. Other workers [33] agree with our observations that the Dare and Tallquist methods (13.8 Gm. per hundred cubic centimeters taken as 100 per cent) frequently give results varying from accurate estimations by as much as 20 per cent, and we have found errors as great

33. Senty, E. G.: A Comparative Study of Various Methods of Hemoglobin Determinations, J. Lab. & Clin. Med. **8**:5 (June) 1923. Brown, G. E.: Prognostic Value of Anemia in Chronic Glomerular Nephritis (chart 1), J. A. M. A. **81**:1949 (Dec. 8) 1923.

as 12 per cent in the estimations made by the new Bausch and Lomb Newcomer hemoglobinometer (16.92 Gm. per hundred cubic centimeters equalling 100 per cent).

We were unable to find any satisfactory data for calculating normal hemoglobin coefficients for males between 19 and 30 years of age at the time our work was started. Recently, however, results have been reported on twenty-seven men. There is a marked difference between the hemoglobin coefficient (13.73 Gm.) reported by Gram and Norgaard [10] on seven men, and the hemoglobin coefficient (15.57 Gm.) reported by Haden [11] on twenty men. This difference probably is due to the small number of cases examined, as all the results fall well within

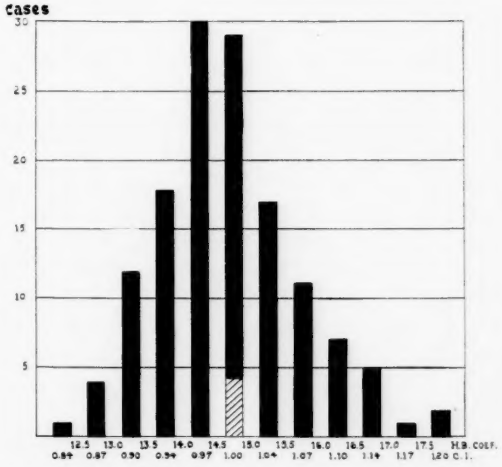

Fig. 4.—Hemoglobin coefficients and color indexes in one hundred and thirty-seven men.

the normal limits of variation determined by us. It may, however, be a national or racial difference, as Gram and Norgaard presumably worked in Denmark and Haden in Kansas City. The average for the twenty-seven men is 15.09 Gm., with extremes of 13.47 and 16.7 Gm.

Our average (on 137 men) of 14.66 Gm. is somewhat less than the average on the twenty-seven men. The average for all the cases (164 men) is 14.73 Gm. Our extremes extend above and below those found in the case of the twenty-seven men examined by others, as might be expected with the larger series of cases. In frequency figure 4 it should be noted that there is a tendency to form a peak in the region of the average, and also that about 90 per cent of the hemoglobin coefficients are between 13 and 16.5, corresponding to color indexes between 0.9 and 1.1. We should expect, therefore, that almost all normal

males between 19 and 30 years of age will yield a color index of from 0.9 to 1.1 on the basis of the normal hemoglobin coefficient determined by us for this sex and age group, i. e., 14.7 Gm.

TOTAL CELL VOLUME

Before comparing the results of different workers, it is necessary to study their methods. These may be divided into three groups, as follows:

1. Methods in which the plasma is not diluted and remains isotonic.

(*a*) Heparin.

(*b*) Hirudin.

2. Methods in which the plasma is diluted but remains isotonic.

(*a*) Three per cent sodium citrate, 1 part added to 9 parts of blood.

(*b*) One and six-tenths per cent sodium oxalate, 1 part added to 10 parts of blood.

3. Methods in which the plasma is not diluted but becomes slightly hypertonic.

(*a*) Potassium oxalate, 20 mg. per ten cubic centimeters of blood.

(*b*) Sodium oxalate, 16 mg. per ten cubic centimeters of blood.

The methods in group 1 are theoretically ideal, but the expense of the hirudin or heparin makes these methods clinically impracticable. The methods in group 2 give satisfactory results, but the blood used for cell volume determination is unsuitable for counts or hemoglobin estimation. The rapidity with which untreated blood must be measured to avoid clotting before mixing with the anticoagulant is apt to lead to inaccuracies. With the methods in group 3 the possibility of shrinkage of the cells must be considered. To determine this point two types of experiments were employed. In the first type portions of well mixed, defibrinated blood were treated as in the methods of groups 2 and 3 with 3 per cent sodium citrate, 1.6 per cent sodium oxalate, and powdered potassium oxalate. As a control another portion was treated with 0.86 per cent sodium chloride in the proportion of 2 parts of saline solution to 10 parts of blood. After fifteen minutes exposure the four samples were centrifugated and freezing point determinations were made in triplicate on each serum. The serums from the bloods treated with sodium citrate, sodium oxalate and sodium chloride solutions all gave a depression of the freezing point of 0.572 degrees. The serum from the blood treated with potassium oxalate crystals gave a depression of 0.654 degrees. The 20 mg. of potassium oxalate increased the osmotic pressure to the same extent that the addition of 13.6 mg. of sodium chloride would have done. In the second type of experiment 30 cc. of human blood was prevented from clotting by mixing with 6 mg. of heparin. Portions of this blood were then treated with

sodium citrate and sodium oxalate solutions, and with powdered potassium oxalate as described in the foregoing. A fourth portion containing only the heparin served as control. These portions were then centrifugated simultaneously to constant volume. The results expressed as cubic centimeters of cells per hundred cubic centimeters of blood in two such experiments follow:

Results by methods of groups 1*a*, 2*a* and 2*b* [34]	30.66 cc.	44.50 cc.
Results using potassium oxalate crystals (group 3)	29.55 cc.	43.00 cc.
Difference	1.11 cc.	1.50 cc.

The difference in volume due to shrinkage is in the first instance 3.6 per cent and in the second instance 3.4 per cent of the volume of unchanged packed cells. This shrinkage is not enough to alter the clinical significance of the volume index figures, even if they were calculated on the basis of a standard volume determined by the methods of groups 1 or 2. As the shrinkage is constant (about 3.5 per cent), if the volume index calculation is based on standards determined by our potassium oxalate method the indexes will be absolutely correct. Since this method is cheaper than those of group 1 and quicker than those of group 2, but just as accurate as the other methods (more accurate if centrifugating to constant volume is disregarded by those using the other methods) it is preferable for clinical use.

Brown and Rowntree,[2] also Keith [35] and his co-workers used methods somewhat similar to our own, but with uncertainty as to the adequacy of the centrifugating. Their results on the sixteen men between 19 and 30 whom they examined average 43.7 cc. of cells per hundred cubic centimeters of blood. No red cell counts were reported. Gram [36] reports twenty-five volume determinations on men, using 3 per cent citrate and centrifugating one and one-half hours at 3,000 revolutions per minute. As he did not give red cell counts, his high average (48 cc. of cells per hundred cubic centimeters of blood) can be explained only by a high average count. Ages were not mentioned. Haden [11] examined twenty men between 19 and 30 years of age. He reports red cell counts. He used 1.6 per cent sodium oxalate. However, since he centrifugated only thirty minutes at 2,500 revolutions per minute the cell volumes of some of his bloods are too high. Therefore, his average volume (46.5 cc.) is too high. The only results by others that seem to be above criticism and that can be fairly compared with our results are those of Gram and Norgaard [10] (hirudin method, centrifugating for one and

34. The dilution with sodium oxalate or sodium citrate solutions did not diminish the time required for complete packing.

35. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

36. Gram, H. C.: A New Method for the Determination of the Fibrin Percentage in Blood and Plasma, J. Biol. Chem. **49**:279 (Dec.) 1921.

one-half hours at 3,000 revolutions per minute) on seven men between 19 and 30. Their average volume was 45.9 cc. The average for our ninety-four men (corrected for the 3.5 per cent shrinkage) is 46.4 cc., a good agreement. The average of the observed volumes on our ninety-four men was 44.84 cc. If Gram and Norgaard's results are brought to the same basis as our results by deducting 3.5 per cent, their average volume becomes 44.3 cc. Further, if their cases are included with our cases, the average for 101 men of this age group becomes 44.8 cc.

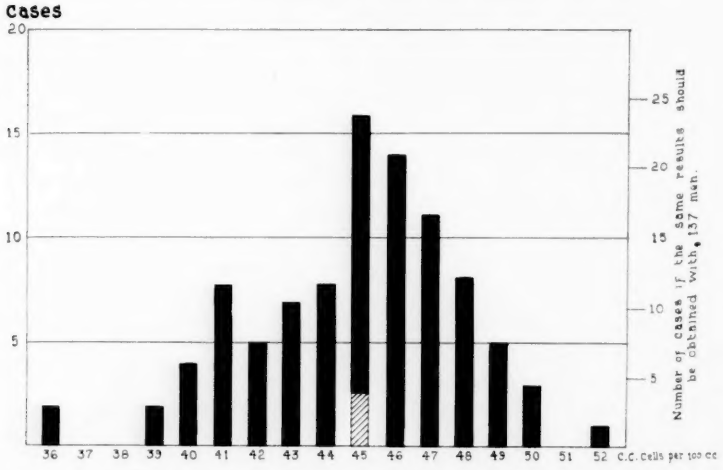

Fig. 5.—Total volume of cells in ninety-four men.

Therefore, we recommend that 45 cc. be considered as the average normal volume of packed cells per hundred cubic centimeters of blood (without reference to the red cell count) when our method is used. Frequency figure 5 shows that there is a definite peak in the region of this average, and that over 90 per cent of the results are between 40 and 50 cc.

VOLUME INDEX

The volume index of a particular blood expresses the ratio between the average size of the red cells in that blood and the average size of the red cells in the blood of healthy persons of the same sex and in the same age group. This index is determined by dividing the volume of the cells expressed as percentage of the average normal volume (100 per cent being considered as the average volume of cells in 100 cc. of blood calculated to a red cell count of 5 million, found in healthy persons of the same sex and age group) by the percentage of red cells (5 million being 100 per cent). We suggest the term *volume coefficient* as a substitute for the awkward expression "volume of packed red cells per hundred

cubic centimeters of blood calculated to a red cell count of 5 million." We use it hereafter with this meaning.

The value of the volume index determination in the differential diagnosis of anemias was first pointed out by Capps [13] and has been emphasized recently by Haden.[11] Volume index determinations cannot be satisfactory for clinical purposes until a good and uniform technic for cell volume estimation has been adopted by all workers. Also, the normal volume coefficients for each sex in the various age groups should be established as soon as possible.

The volume coefficients calculated from our data (ninety-four men between 19 and 30 years of age) average 40.8, varying from 34.5 to 46. These extremes correspond to volume indexes of from 0.86 to 1.12. Gram and Norgaard [10] report the only satisfactory volume coefficients

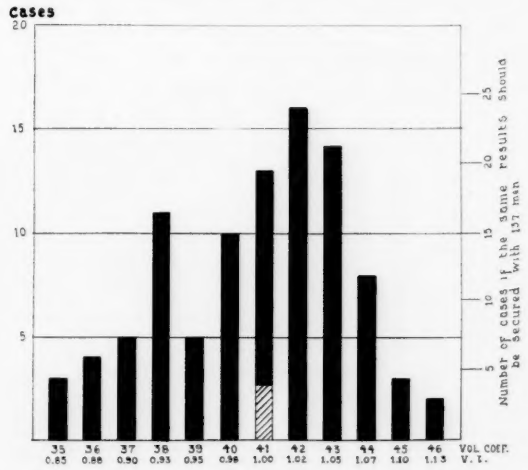

Fig. 6.—Volume coefficients and volume indexes in ninety-four men.

we were able to find in the literature, but they examined only seven men in this age group. If 3.5 per cent is deducted from their average to make their results comparable to ours, their figure, 41, agrees very well with ours, 40.8. We also mention Haden's [11] results on twenty men (from 18 to 30 years of age), although we believe his average, 45.92, is too high. He neglected to centrifugate to constant volume, and our experience has shown that his thirty minute period of centrifugating at 2,500 revolutions per minute is not sufficient to pack the cells of many normal bloods completely. Sedimentation times of normal bloods vary markedly, and some are high. Therefore, if actual cell volume is to be determined we cannot overemphasize the importance of centrifugating to constant volume.

The average volume coefficient for 101 men (excluding Haden's results) is 40.8. Therefore, we make the tentative recommendation that 41.0 be used as the normal volume coefficient for men between 19 and 30 years of age when our technic is used. The frequency distribution of volume coefficients and of the volume indexes of the blood of our ninety-four men is shown in figure 6. The volume indexes are calculated on the basis of a volume coefficient of 41 as 100 per cent. It will be seen that over 90 per cent of the volume coefficients fall between 37 and 45, that is, between volume indexes of 0.9 and 1.1.

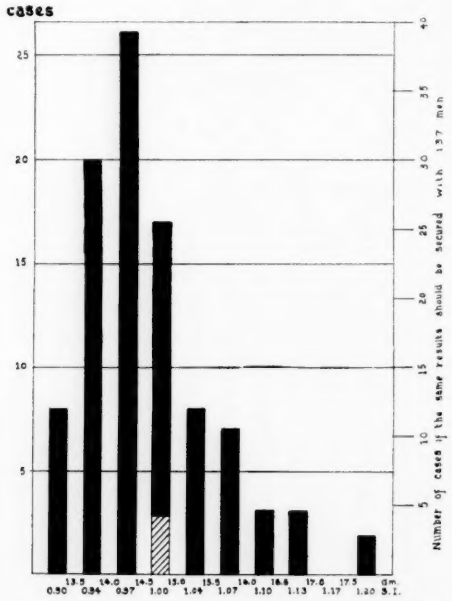

Fig. 7.—Grams of hemoglobin per 41 cc. of cells and saturation indexes in ninety-four men.

SATURATION INDEX

Haden [11] coined the term saturation index for the figure expressing the ratio between the concentration of hemoglobin per unit volume of cells in a particular subject and the average concentration of hemoglobin per unit volume of cells in normal subjects of the same sex and age group. It is most easily calculated by dividing the color index by the volume index.

Sufficient data for calculation of saturation indexes are reported by Gram and Norgaard [10] for seven men and by Haden [11] for twenty men.

Their results are not comparable with ours because their technic for cell volume determination differs from ours.

In figure 7 are plotted the grams of hemoglobin per 41 cc. of packed cells in the blood of our ninety-four men. It will be noticed that there is a tendency to form a peak in the region of the average (14.6 Gm.),[37] and that over 90 per cent of the results fall between 13 and 16.5 Gm., corresponding to saturation indexes of 0.9 to 1.1.

FURTHER STUDIES SUGGESTED

Our work has suggested so many lines of investigation that are made possible by the methods we have used that it seems best to outline some of the more important.

1. What are the normal hemoglobin, color index and volume index standards for other age groups of both sexes? We have made a start toward duplicating our investigations by work on women between 19 and 30 years of age. We hope to report this in the near future. The literature is meager and unsatisfactory for other age groups. Practically no work has been done on volume index or saturation index determinations in children. These problems simply require repetition of the technic described here. Obviously the results of such investigations are certain to be of value.

2. Are there racial or geographical differences (aside from altitude) in these blood findings? In our German and Scandinavian students we have noted a tendency toward a red cell count in the higher ranges, with a volume index and color index in the lower ranges of the normal. This would indicate red cells of small size. The number of these men in our series was too small to be of any statistical value, however. If such a tendency does exist, it would account for the low hemoglobin coefficients that continue to be reported from those countries. Our results also require confirmation by work on those living in other parts of the United States and Canada.

3. Is there a marked diurnal variation in the hemoglobin content of the blood of normal persons as claimed by Dreyer,[38] Ward[39] and Rabinowitch?[40] If so, is this accompanied by corresponding changes in red cell count and cell volume? More complete examinations checked with control estimations to show the limits of error in the technic are

37. This figure agrees well with the hemoglobin coefficient (14.66 Gm.) found in the group of 137 men. The figures would, of course, be identical if they were derived from exactly the same series of cases.

38. Dreyer, G.; Bazeth, H. C., and Pierce, H. F.: Diurnal Variations in the Hemoglobin Content of the Blood, Lancet **199**:588 (Sept. 18) 1920.

39. Ward, H. C.: The Hourly Variations in the Quantity of Hemoglobin and in the Number of the Corpuscles in Human Blood, Am. J. Physiol. **11**:394 (July) 1904.

40. Rabinowitch, I. M.: J. Lab. & Clin. Med. **9**:120 (Nov.) 1923.

needed to confirm these reports. The hemoglobin estimations reported by Rabinowitch [39] are too low to be comparable to our results. If such variations do occur it may be advisable to draw the blood before breakfast as is done for blood chemistry work.

4. Is there a seasonal variation in the hemoglobin content and in the number of erythrocytes of blood as is asserted in some texts? The fact that we found no significant seasonal variations in our group is not sufficient evidence. Daily complete blood studies should first be made on a group of normal persons to determine the amount of variation to be expected within one season. Then, throughout the year, weekly or biweekly examinations should be made on the bloods of the same persons. The climatic conditions should be studied in connection with this work. The blood for these examinations should preferably be taken at the same hour before breakfast.

TABLE 3.—*Classes of Anemia*

	Group	Color Index	Volume Index	Saturation Index	Possible Diagnostic Significance
Volume index and color index vary in proportion to one another (saturation index normal)	..	From 0.85 to 1.15	From 0.85 to 1.15	From 0.85 to 1.15	Normals
	1	Less than 0.85	Less than 0.85	From 0.85 to 1.15	Hemolytic type of secondary anemia
	2	More than 1.15	More than 1.15	From 0.85 to 1.15	Uncomplicated pernicious anemia
	3	From 0.85 to 1.15	From 0.85 to 1.15	From 0.85 to 1.15	Aplastic anemia and anemia of acute blood loss
Volume index higher than color index (saturation index low)	4	Less than 0.85	Somewhat less than 0.85	Less than 0.85	Anemia of chronic blood loss
	5	Less than 1.15	More than 1.15	Less than 0.85	Pernicious, with coexisting secondary anemia
	6	Less than 0.85	From 0.85 to 1.15	Less than 0.85	Chlorosis and chlorotic type secondary anemia
Volume index lower than color index (saturation index high) (probably does not occur)	7	From 0.85 to 1.15	Less than 0.85	More than 1.15	
	8	More than 1.15	From 0.85 to 1.15	More than 1.15	Obsolete views of the blood findings in pernicious anemia
	9	More than 1.15	Somewhat more than 1:15	More than 1.15	

5. May it not be possible for diagnostic purposes to subdivide anemias according to their color indexes, volume indexes and saturation indexes? No work on the clinical value of the saturation index has been reported. A little work has been done on volume index which, if confirmed, makes a high volume index the most valuable single laboratory finding in the diagnosis of pernicious anemia. We have, as yet, made a thorough study of only sixty-three cases of anemia. In fifteen of these cases the volume index was high and the diagnosis of pernicious anemia was established. Two other cases showed high volume indexes, but the diagnosis of pernicious anemia has not yet been made by the clinician; both of these must be followed for a longer time.

Nine classes of blood disorders are theoretically possible (table 3). We suggest this tentative classification only as a working basis for group-

ing large numbers of carefully studied cases of anemia. Groups 7, 8 and 9 probably do not occur, although this has not been adequately proved. Of the other groups, we have studied no cases in group 6 (this group probably occurs) and only one case in group 1. Our experience with the other sixty-two cases of anemia leads us to believe that we have attributed the proper diagnostic significance to the findings in groups 2, 3, 4 and 5. We hope that the diagnostic significance of this classification will be confirmed or amended in the near future.

TABLE 4.—*Averages and Range of Variation in Normal Findings in One Hundred Thirty-Seven Men*[41]

	Average	Range of Results
Red cell count	5.4	90 per cent, from 4.7 to 6.1 million per cubic millimeter
Total hemoglobin	15.8	90 per cent, from 14 to 18 gm. per hundred cubic centimeters
Hemoglobin coefficient	14.7	
Color indexes	1.0	90 per cent, from 0.9 to 1.1
Total volume of cells	45.0	90 per cent, from 40 to 50 cc. per hundred cubic centimeters
Volume coefficient	41.0	
Volume indexes	1.0	90 per cent, from 0.9 to 1.1
Saturation indexes	1.0	90 per cent, from 0.9 to 1.1

SUMMARY

1. The bloods of 137 men from 19 to 30 years of age have been studied for the purpose of establishing standards for the normal averages and determining the range of variation in normal findings (table 4). A review of the literature covering the same points for normal men of the same age group is presented.

2. The term *hemoglobin coefficient* is proposed as a substitute for "the amount of hemoglobin in grams per hundred cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeter." This is the figure used as 100 per cent hemoglobin in calculating color indexes.

3. Similarly, the term *volume coefficient* is proposed to take the place of "the volume of packed red cells in cubic centimeters in 100 cc. of blood calculated to a red cell count of 5 million per cubic millimeter." This is the figure used as 100 per cent cell volume in calculating volume indexes.

4. The term saturation index was proposed by Haden to express the ratio between the average hemoglobin content per unit volume of cells in the blood examined and the average hemoglobin content per unit volume of cells in the blood of normal persons of the same sex in the same age group. Our method of calculating saturation indexes by dividing the color index by the volume index is simpler than Haden's method of calculation.

41. The altitude at the place of estimation is not over 500 feet.

5. Figures 2 to 7 have been so constructed that one may see at a glance the frequency distribution and the extremes for each type of finding.

6. The methods employed are practical for clinical as well as research use. Our method of centrifugating to constant volume simplifies and increases the accuracy of volume index determinations.

7. The hematocrit is not a reliable substitute for hemoglobin estimations or for red cell counts.

8. The use of oxalated venous blood (20 mg. of powdered potassium oxalate per 10 cc.) is advised for all work, including red cell counts.

9. A tentative classification of anemias on the basis of color index, volume index and saturation index is suggested.

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ESTIMATION OF TRANSVERSE CARDIAC DIAMETER IN MAN*

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In recent years the employment of roentgenologic methods has been advocated by numerous writers as a means of developing greater accuracy in the field of cardiac diagnosis. Notable among these have been Vaquez and Bordet [1] and their co-workers in France, who have been largely responsible for the perfection of the orthodiascopic technic which has been so successful in their hands.

Various measurements of the cardiac silhouette as obtained by teleoroentgenographic or orthodiagraphic methods have been proposed, but in more recent times, following the work of Bardeen,[2] these have usually been restricted to two, the area of the silhouette and its greatest transverse diameter. Cardiac area as determined by the planimeter measurement of the orthodiagraphic or teleoroentgenographic tracings is a measurement that can be made with surprising accuracy despite the fact that several writers have expressed doubt as to the ability of even the most experienced observer accurately to complete the more or less arbitrary upper and lower heart borders.

In the hands of one with experience in this work, the results from the same subject on different occasions check closely [3] and different observers using the same tracings usually obtain variations of only a few square centimeters in area. The orthodiagraphic method increases the accuracy of area measurements by giving somewhat more of the cardiac border than it is possible to obtain from films. In the determination of exact transverse diameter measurements from cardiac shadows, however obtained, the points between which the distance is taken are always to be found on the unobstructed cardiac contours, thereby reducing the personal factor to a negligible minimum. The fact that a heart of a given size will show a narrow transverse diameter if suspended more or less freely in a long chest, or a wide diameter if pushed upward into a transverse position by an elevated diaphragm cannot so easily be accepted as compatible with the use of this measurement as a valuable index of cardiac normality or pathology. If one were able to show, however, that transverse cardiac diameter in individuals free from

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1. Vaquez, H., and Bordet, E.: The Heart and the Aorta, translated from the French by Honeij and Macy, Yale University Press, 1920.

2. Bardeen, C. R.: Determination of the Size of the Heart by Means of the X-Rays, Am. J. Anat. **23**:423-487 (March) 1918.

3. Eyster, J. A. E., and Evans, J. S.: **Tr.** A. Am. Phys., 1923.

cardiac disease of any sort bears a constant relationship to one or more body measurements which can be readily and accurately obtained, this relationship could be advantageously used to predict in which individuals the heart may be expected to lie transversely and in which vertically, or, in other words, to predict with some accuracy the most probable diameter in any given individual. The existence and extent of such relationship can be determined by the method of statistical analysis known as the correlation of a criterion (in this case transverse diameter of the normal heart) with one or more variables (such as height and weight).

Laborious as we beginners in this field of analysis find the required mathematical procedures so widely used by the medical psychologists, the results of such endeavor are well worth the effort, for such a study of otherwise abstruse data permits of their accurate and positive interpretation. For instance, at first thought one might be so impressed by the effect of diaphragm level in determining cardiac position as to suppose that in tall persons with long chests one will find a predominance of narrow diameters. In this assumption he will be partially correct, but by analyzing a group of normal cases by the method suggested, we can say with certainty that the inverse relationship of height to transverse diameter is slight as compared to the direct proportion of transverse diameter to weight, thus showing that weight is the better index to transverse diameter.

In the early days of calorimetry the clinical value of accurate basal metabolism figures was greatly discounted by the lack of accurate means of estimation of the probable normal heat production for a given subject, and only when prediction tables for normal caloric output were made available did indirect calorimetry become a practical diagnostic procedure. The situation with regard to the use of the roentgen ray in cardiac disease has, in the past, been very similar as the roentgenologic technic in this field has developed rapidly, whereas prediction methods have scarcely kept pace. In 1918 Bardeen [2] published his now well known tables of normal measurements, but it was not until 1924 that P. C. Hodges and one of us (J. A. E. E.[4]) published a new set of prediction tables for cardiac area only, which were based on the statistical study of normal data and which, therefore, give optimal values for all variable factors. As would be expected, these tables show somewhat greater accuracy when analyzed mathematically, and present a method of prediction comparable to the well known prediction tables for basal metabolism.

The following data have been stripped of their mathematical understructure, and are presented in more or less tabloid form because exactly

4. Hodges, P. C., and Eyster, J. A. E.: Estimation of Cardiac Area in Man, Am. J. Roentgenol. **12**:252-265 (Sept.) 1924. This article contains a useful bibliography of the subject.

TABLE 1.—*Original Data*

Case	Age	Height	Weight	Cardiac Area	Transverse Diameter
1	34	170	53	91	97
2	18	180	68	113	102
3	28	175	64	91	105
4	28	173	61	102	105
5	28	168	54	98	107
6	31	170	75	103	107
7	46	168	72	82	107
8	28	185	60	93	108
9	33	173	57	93	108
10	30	175	72	101	109
11	33	178	67	105	110
12	25	180	68	107	110
13	45	178	64	112	111
14	28	178	62	102	112
15	32	173	64	108	112
16	26	175	66	106	113
17	27	185	78	126	113
18	33	183	73	102	113
19	29	178	62	115	113
20	32	173	67	110	113
21	30	178	64	107	114
22	27	178	68	113	114
23	25	183	63	106	114
24	28	175	68	105	114
25	27	173	70	113	115
26	23	175	64	125	115
27	20	179	62	115	115
28	30	170	67	92	115
29	28	168	55	99	115
30	32	170	70	104	115
31	23	163	56	92	115
32	34	175	76	112	116
33	18	176	62	110	117
34	32	168	64	117	117
35	31	180	68	115	117
36	19	173	66	118	119
37	33	178	74	117	120
38	24	159	55	103	120
39	26	173	64	110	120
40	26	170	60	119	121
41	46	170	74	105	121
42	30	163	61	103	121
43	33	165	60	106	122
44	30	168	67	104	122
45	22	175	66	124	123
46	47	182	82	124	124
47	30	180	70	118	125
48	27	175	72	113	125
49	43	183	84	122	125
50	28	164	62	106	126
51	34	173	64	119	126
52	29	180	84	96	126
53	24	185	68	117	126
54	37	192	77	143	127
55	33	179	66	112	127
56	37	192	77	143	127
57	30	178	70	123	128
58	28	175	74	115	129
59	59	170	57	117	129
60	26	175	73	119	130
61	28	178	75	117	130
62	30	173	77	108	131
63	33	168	68	100	131
64	34	173	64	135	132
65	27	174	85	105	132
66	25	173	68	118	134
67	45	171	79	113	134
68	50	183	77	143	135
69	26	183	77	128	136
70	33	179	70	139	136
71	27	178	73	113	136
72	29	178	73	120	137
73	28	172	61	124	137
74	29	178	75	129	139
75	35	173	75	112	139
76	52	178	79	136	140
77	35	175	79	128	140
78	31	180	83	121	142
79	34	185	98	123	142
80	34	179	86	132	147
Total	2,488	14,037.1	5,533.0	9,015	9,742
Mean	31.100	175.463	69.162	112.687	121.775
Sigma	7.4020	6.0785	8.3669	...	10.9109

the same formulas have been adapted to this work which were previously presented so completely by P. C. Hodges and one of us (J. A. E. E.). The various preliminary coefficients necessary for the formulation of the final equation will be found systematically listed in a footnote for the benefit of those desiring to follow the mathematics step by step. In the prediction tables which present the results of this work in a usable form, the previously published tables for area have been incorporated for the sake of convenience.

DATA

The original seventy cases from the measurements of which P. C. Hodges and one of us (J. A. E. E.) computed the prediction formula for cardiac area, augmented by ten additional normals, have been used as a basis for transverse diameter estimation. The selection of these cases was based, as before, in every instance on an exhaustive physical examination, including history, roentgen-ray studies and electrocardiograms, and no case with any suggestion of cardiac abnormality, whether accidental murmur, occasional ventricular extrasystole or simply sinus arrhythmia was included. All of the subjects are males, taken from the student body of the University of Wisconsin, the group of cases examined for the U. S. Veterans Bureau and from private practice.

In order to determine the correlation of the criterion, in this case transverse diameter, with all other variables when each has been given its optimal value, an interesting group of zero order coefficients must first be obtained. These correlations show the relationship between every possible pair of variables, and will be found listed in Table 2. Perfect correlation or parallelism between any two factors is indicated as unity (1.0). Obviously perfect correlation is not to be expected between any two variables in a study such as this, a correlation of 0.5 or better being considered good. It will be noted that of all the variables, weight has the greatest effect on (the best correlation with) transverse diameter, its actual figure being 0.5738. Age, which shows the next best correlation, is far less important than weight in determining transverse diameter, for its figure is only 0.2371. Height is of still less value with a correlation of 0.2140.

It is interesting to note at this point that in developing the formula for cardiac area P. C. Hodges and one of us (J. A. E. E.) found height to correlate best with the criterion, 0.5337; weight next, with 0.4533; and age last, with 0.1241. Probably the fact that height is the most important single factor in determining area is largely responsible for the low degree of inverse proportion between height and transverse diameter, because tall subjects having greater area show, therefore, wider diameter irrespective of heart position. Valuable as these simple correlations are in yielding concrete information as to the relative effect of body measure-

ments on the measurement we are studying, they can be used to far greater advantage by carrying the mathematics further and developing in succession correlations of increasing complexity until by substituting these values in a regression equation a formula is obtained by which one is enabled to estimate the most probable transverse diameter in any given individual by assigning to his age, height and weight measurements their optimal value in affecting transverse diameter. This formula is devel-

TABLE 2.—*Outline of Mathematical Treatment of Data*

	Means	Squares of Means	Means of Squares	Sigmas
Age	31.1	967.21	1,022.000	7.4020
Height	175.463	30,787.2644	30,824.212	6.0785
Weight	69.162	4,783.3822	4,853.387	8.3669
Transverse diameter	121.775	14,829.1506	14,948.200	10.9109
Predicted transverse diameter	121.787	14,832.073	14,876.462	6.6625

$M_{T\text{-}D} \times A = 3,806.350$
$M_{T\text{-}D} \times H = 21,381.075$
$M_{T\text{-}D} \times W = 8,474.587$
$M_{A} \times H = 5,459.7875$

$M_{A} \times W = 2,168.3750$
$M_{H} \times W = 12,161.7000$
$M_{T\text{-}D} \times P = 14,872.762$

Zero Order Correlation Coefficients

$r_{T\text{-}D\ A} = 0.2371$
$r_{T\text{-}D\ H} = 0.2140$
$r_{T\text{-}D\ W} = 0.5738$
$r_{A\ H} = 0.06421$
$r_{A\ W} = 0.2816$
$r_{H\ W} = 0.5177$

First Order Coefficients

$r_{T\text{-}D\ A.W} = 0.0962$
$r_{T\text{-}D\ H.W} = -0.1189$
$r_{A\ H\ .\ W} = -0.0995$
$r_{H\ W\ .\ A} = 0.5329$
$r_{T\text{-}D\ W.H} = 0.5553$
$r_{T\text{-}D\ A.H} = 0.2292$

$r_{A\ W\ .\ H} = 0.291a$
$r_{T\text{-}D\ W.A} = 0.5433$
$r_{A\ H.T\text{-}D} = 0.0143$
$r_{T\text{-}D\ H.A} = 0.2088$
$r_{A\ W.T\text{-}D} = 0.1830$
$r_{H\ W.T\text{-}D} = 0.4947$

Second Order Correlation

$r_{T\text{-}D\ A\ .\ H\ W} = +0.0854$
$r_{T\text{-}D\ H\ .\ A\ W} = -0.1106$
$r_{T\text{-}D\ W\ .\ A\ H} = +0.5244$
$r_{A\ W\ .\ T\text{-}D\ H} = +0.2027$
$r_{H\ W\ .\ T\text{-}D\ A} = +0.5117$

Partial Standard Deviation

$S\ .\ D\ T\text{-}D\ .\ A\ H\ W = 10.3664$
$S\ .\ D\ A\ .\ T\text{-}D\ H\ W = 7.0437$
$S\ .\ D\ H\ .\ T\text{-}D\ A\ W = 5.1424$
$S\ .\ D\ W\ .\ T\text{-}D\ A\ H = 5.7865$

Validity of Prediction

$r_{T\text{-}D\ .\ A\ H\ W} = 0.587707$ (direct order)
$r_{T\text{-}D\ .\ A\ H\ W} = 0.586856$ (indirect order)
$r_{T\text{-}D\ P}$ (zero order correlation between measured and predicted T-D) $= 0.579$

Probable error of distribution $= 7.36$
Probable error of estimate $= 4.82$
Efficiency of prediction $= 1 - \sqrt{1 - R^2} = 19\%$

oped by the Thurstone-Hull method and, based on the data taken from the original eighty cases, is written:

Predicted $TD = +0.1094 \times A - 0.1941 \times H + 0.8179 \times W + 95.8625$, in which TD equals transverse diameter, A, age, H, height, and W, weight. This formula or equation can be translated into the following language: The probable normal cardiac transverse diameter of any male subject can be most accurately estimated by adding the products of

0.1094 × age, 0.8179 × weight, subtracting from this sum the product of 0.1941 × height and adding to the remainder the fixed figure 95.8625.

For the sake of convenience the effect of age on transverse diameter has been computed for the various decades of life and since the effect of age is so slight as to make little difference in the final figure, the simple procedure of adding to the height-weight values 1 mm. of transverse diameter for every decade can be employed without loss of accuracy. Again for the sake of convenience the factor for height (— 0.1941) has been multiplied by the entire range of figures from 150 to 200 cm. and the constant 95.8625 has been added to each of these and the final figures listed in tabloid form. Another portion of this table lists all weights between 50 and 100 Kg. each multiplied by the weight factor (0.8179). This table makes possible the ready computation of transverse diameter predictions by simply adding to the transverse diameter value opposite the correct weight figure the transverse diameter value opposite the height figure, and adding one more millimeter for each decade of age.

The formula on which these tables are based permits of mathematical verification by the following method: The correlation of the criterion, *TD*, with the entire team of variables when each of these variables is given its optimal weight gives a figure that represents the degree of parallelism between the entire combination of variables and the criterion. This figure can be obtained by solving two similar equations, the only difference being the order in which values are introduced. If these two figures are identical or approximate each other closely one can be sure that no gross errors in arithmetic exist. The two figures so obtained are 0.587 and 0.588. If one applies the finished prediction formula to the original cases studied and then correlates the predicted transverse diameters against the measured transverse diameters, it will be seen that a correlation value should result which is identical with the figures just given. When this is done in this problem, correlation between *TD* and *P* (predicted transverse diameter), the resulting figure reads 0.579, showing a discrepancy easily explained by the dropping of decimals.

It can be readily understood that the more closely this final correlation figure approximates unity, the more efficient will be the prediction formula itself, for if we were able by any formula to predict the exact normal transverse diameter in every case the correlation between predicted values and measured values would be 1.0, or perfect correlation. It is perfectly true that 0.58 represents only fair prediction ability, and yet it can be shown that this method definitely decreases the probable error which would exist if one depended entirely on pure guesswork for estimating normal diameter. As a matter of fact, the efficiency of this formula is 19 per cent, which means that it is 19 per cent more efficient than assuming an average for all cases. Expressed in other

words, the probable error of distribution, where guesswork is employed, is 7.36, whereas the formula reduces this error to a probable error of estimate of 4.82.

It is evident from the foregoing that this formula, as well as all other available means for predicting normal cardiac measurements,

TABLE 3.—*Prediction for Normal Cardiac Area and Transverse Diameter*

Predicted T-D = +0.1094 × A − 0.1941 × H + 0.8179 × W + 95.8625

I				II			
Stature		Area, Sq. Cm.	Transverse Diameter, Mm.	Weight		Area, Sq. Cm.	Transverse Diameter, Mm.
Cm.	In.			Kg.	Pounds		
150	59	66.7	66.74	50	110	17.00	40.90
151		67.57	66.55	51	112.2	17.34	41.71
152	60	68.44	66.36	52	114.4	17.68	42.53
153		69.31	66.16	53	116.6	18.02	43.35
154		70.18	65.97	54	118.8	18.36	44.17
155	61	71.05	65.77	55	121	18.70	44.98
156		71.92	65.58	56	123.2	19.04	45.80
157		72.79	65.39	57	125.4	19.38	46.62
158	62	73.66	65.19	58	127.6	19.72	47.44
159		74.53	65.00	59	129.8	20.06	48.26
160	63	75.40	64.80	60	132	20.40	49.07
161		76.27	64.61	61	134.2	20.74	49.89
162		77.14	64.42	62	136.4	21.08	50.71
163	64	78.01	64.22	63	138.6	21.42	51.53
164		78.88	64.03	64	140.8	21.76	52.35
165	65	79.75	63.83	65	143	22.10	53.16
166		80.62	63.64	66	145.2	22.44	53.98
167		81.49	63.45	67	147.4	22.78	54.80
168	66	82.36	63.25	68	149.6	23.12	55.62
169		83.23	63.06	69	151.8	23.46	56.44
170	67	84.10	62.86	70	154	23.80	57.25
171		84.97	62.67	71	156.2	24.14	58.07
172		85.84	62.47	72	158.4	24.48	58.89
173	68	86.71	62.28	73	160.6	24.82	59.71
174		87.58	62.09	74	162.8	25.16	60.52
175	69	88.45	61.89	75	165	25.50	61.34
176		89.32	61.70	76	167.2	25.84	62.16
177		90.19	61.50	77	169.4	26.18	62.98
178	70	91.06	61.31	78	171.6	26.52	63.80
179		91.93	61.12	79	173.8	26.86	64.61
180	71	92.80	60.92	80	176	27.20	65.43
181		93.67	60.73	81	178.2	27.54	66.25
182		94.54	60.53	82	180.4	27.88	67.07
183	72	95.41	60.34	83	182.6	28.22	67.89
184		96.28	60.15	84	184.8	28.56	68.70
185	73	97.15	59.95	85	187	28.90	69.52
186		98.02	59.76	86	189.2	29.24	70.34
187		98.89	59.56	87	191.4	29.58	71.16
188	74	99.76	59.37	88	193.6	29.92	71.98
189		100.63	59.18	89	195.8	30.26	72.79
190		101.50	58.98	90	198	30.60	73.61
191	75	102.37	58.79	91	200.2	30.94	74.43
192		103.24	58.59	92	202.4	31.28	75.25
193	76	104.11	58.40	93	204.6	31.62	76.06
194		104.98	58.21	94	206.8	31.96	76.88
195		105.85	58.01	95	209	32.30	77.70
196	77	106.72	57.82	96	211.2	32.64	78.52
197		107.59	57.62	97	213.4	32.98	79.34
198	78	108.46	57.43	98	215.6	33.32	80.15
199		109.39	57.23	99	217.8	33.66	80.97
200	79	110.20	57.04	100	220	34.00	81.79

To find normal transverse diameter for a given individual, add T-D figure for stature to T-D figure for weight and to this total add 1 mm. for every decade of age; e. g., height, 6 feet; weight, 187 pounds; age, 50 = 134.86 mm. T-D or 60.34 + 69.52 + 5.

leaves much to be desired in the way of efficiency, for 19 per cent is, at best, only a slight improvement over random guessing. There is, of course, a definite possibility of improving the efficiency of the formula, but the data in hand is insufficient to accomplish this. What one must

have in order to improve the formula is a new variable which correlates weakly with age, height and weight, and at the same time strongly with the transverse diameter. Variables that suggest themselves are girth, anteroposterior chest diameter and vital capacity. Undoubtedly, these will bear testing and it is possible that some one of these will be of value, though there is already information available to show that all of these measurements bear a fairly close relationship to height and weight, and if their intercorrelation figures are high as compared to their individual correlations with transverse diameter, their addition to the formula will be of slight value.

It remains to be seen by comparing the measurements of a group of known pathologic hearts with these tables just how great an individual deviation from predicted normal one must obtain to diagnose with certainty the existence of pathology in any one subject. However, by making use of Thorndike's tables based on a population of 10,000 people, the results of transverse cardiac diameter prediction in a large group can be demonstrated in advance. If we suppose that one were to find after predicting from age, height and weight in 10,000 persons that our formula (with its probable error of 4.82 mm.) had assigned to each a transverse cardiac diameter value of 100 mm., the actual measurement of these same subjects by othodiagraphic means would show 5,000 hearts between 95 and 105 mm.; 2,500 hearts larger than 105, and 2,500 hearts smaller than 95. Three-fourths of these cases, therefore, would not exceed 100 mm. by more than 5 mm., or conversely the odds would be three to one against a normal subject having a measured cardiac transverse diameter that would exceed his predicted diameter by more than 5 mm.

SUMMARY

1. New tables are presented for the estimation of normal transverse cardiac diameter in man. These tables are based on the following prediction formula: Transverse diameter in millimeters equals age 0.1094 — stature 0.1941 + weight 0.8179 + the constant 95.8625.

2. The tables given here introduce a means of prediction that is 19 per cent efficient.

3. New variables that have but slight relation to age, height and weight while paralleling transverse diameter rather closely must be sought in order to improve this formula.

4. If the heart is found to be 5 mm. wider in its greatest transverse diameter than the diameter as predicted by this formula, the chances are three to one that the widening is pathologic.

THE EFFECT OF LEAD AND RADIUM ON MATURE AND IMMATURE RED BLOOD CORPUSCLES*

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The epoch making discoveries of the roentgen rays by Roentgen and of radium by the Curies have lead rapidly to much knowledge of vital processes and to the alleviation of disease. One of the must useful clinical applications of these radiations is in the therapy of cancer. The application of radio-active substances does not always result in destruction of the tumor, but their beneficial effects are such as to warrant the search for a means of increasing their destructive properties. It has been suggested that this may be accomplished by introducing into the tissue some substance to augment the production of secondary radiation. Lead, among other substances, has been tried in the belief that it enters cancer tissue and young cells more readily than normal tissue or adult cells.

For determining the effect of irradiation on tissues, with and without the presence of substances causing secondary radiations, animal cancer transplants are unsatisfactory. The great variations in the rate and duration of growth and reaction to treatment of these neoplasms is well known and makes the interpretation of the effect of therapy both difficult and uncertain. It was decided, therefore, to determine if information could be obtained from a study of blood cells to warrant further consideration of the problem. Erythrocytes furnish suitable test cells for this purpose. This is because not only may they be obtained in varying degrees of maturity but also their hemolysis furnishes a quantitative index of cell destruction. It is recognized that the behavior of immature, as contrasted with adult red blood corpuscles, does not necessarily indicate that a similar action occurs with cancer and normal tissue cells.

METHOD

The effect of lead, radium emanation and combinations of the two was tested on mature and immature red blood cells in various ways. Each of the experiments recorded was repeated not less than five times to insure the correctness of the observations.

Normal rabbits were rendered anemic by repeated withdrawal of blood from the heart. Previous to and during the period of bleeding

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observations were made on the red blood cell count, the percentage of hemoglobin and reticulocytes, and the "fragility" of the red cells in hypotonic sodium chlorid solutions. It was hoped to obtain a comparison of effects of the substances on the reticulated and the adult red corpuscles from the blood of the same animal. This was attempted repeatedly but was found to be impracticable. Therefore, when the blood contained from 30 to 50 per cent reticulated erythrocytes it was used for a comparison with that of a normal rabbit whose blood consisted almost entirely of adult cells. The term "immature cells" is used in the text to denote erythrocytes obtained from a rabbit whose blood contained more than 30 per cent reticulocytes. The term "adult cells" is used to indicate red blood corpuscles obtained from an animal having less than 3.5 per cent reticulated erythrocytes in the peripheral circulation.

Approximately 30 cc. of blood were withdrawn from a normal rabbit and shortly afterward from an anemic rabbit. The tests referred to above were made on each specimen. These bloods were gently defibrinated, washed serum free with modified Ringer's solution,[1] and suspended in it in a concentration of approximately 40 per cent. Each of these two suspensions of corpuscles then was divided into four equal portions. The first was allowed to stand in the Ringer's solution for the duration of the experiment and served as a control. The second was exposed to an equal volume of 0.001 per cent lead chlorid solution for one hour, which, as has been shown by Aub, Reznikoff and Smith,[2] is sufficient to "lead" red cells. These cells were then washed free of the lead solution and resuspended in Ringer's solution for the remainder of the experiment. The third fraction was similiarly treated with lead and after being washed was exposed to radium emanation. The fourth portion was irradiated only.

The red cells in each of the eight samples, after being washed, were subjected to various strengths of hypotonic salt solution to test their resistance to hemolysis. This test was conducted as follows: One cubic centimeter portions of sodium chlorid solutions, ranging in strength from 0.9 to 0.04 per cent with a variation of 0.02 per cent between each solution, were placed in test tubes. To each was added 0.15 cc. of a 20 per cent suspension of cells. After these preparations had stood in the cold for ten hours the percentage of hemolysis was determined by direct comparison with standards.

Suspensions of each of the eight different samples also were allowed to stand for ten hours in the cold. The percentage hemolysis then

1. The Ringer's solution was carbonate and phosphate free and contained sodium chlorid, 0.9 per cent., potassium chlorid, 0.042 per cent., and calcium chlorid, 0.024 per cent.

2. Aub, J. C.: Reznikoff, P., and Smith, D. E.: Lead Studies, III, The Effects of Lead on Red Blood Cells, J. Exper. Med. **40**:151 (Aug.) 1924.

resulting was determined by comparison with standards in a Duboscq colorimeter.

All solutions were maintained as near as possible at p_H 6.5.

The radio-active substance used was radium emanation collected and purified by the method of Duane [3] and contained in evacuated tubes of 1 by 6 cm. size, which were drawn out to a capillary tip at either end. These tubes were allowed to stand overnight before the cells were exposed to allow the emanation to reach an equilibrium with its decomposition products. The quantity of the emanation was then measured by means of the method and apparatus described by Duane.[3] One of these tubes was immersed beneath the surface of the cells suspension; its capillary tip was broken off, and the suspension was carried into the tube by negative pressure. The broken tip was immediately sealed with paraffin. From time to time the tube was gently agitated to insure a uniform mixture of the contents. This is, in all essentials, the method described and used by Redfield and Bright,[4] and since the emanation is in solution it affords a convenient method of irradiating fluids. As the alpha, beta and gamma rays all act on cells in suspension, doses of only one millicurie hour are required. Whenever results were to be compared the same amount of emanation was used.

THE "FRAGILITY" OF ERYTHROCYTES TO HYPOTONIC SODIUM CHLORID SOLUTIONS

1. *Controls.*—It was noted that the erythrocytes from rabbits rendered anemic by chronic blood loss were invariably more resistant to hypotonic salt solution than the cells of the same rabbit prior to bleeding. This is in accord with and confirmatory of the results obtained by Minot and Weld.[5] Apparently it is one of nature's provisions for the preservation of a competent circulating blood after prolonged hemorrhage.

Likewise, it was noted that there is a difference in the resistance of the erythrocytes to hypotonic salt solutions immediately and some time after their withdrawal from the circulation. Cells that have stood several hours are less easily hemolyzed than those which have been obtained recently from the circulating blood. This phenomenon was observed constantly and is in accord with the work of Ashby [6] and others. Thus,

3. Duane, W.: Methods of Preparing and Using Radio-Active Substances in the Treatment of Malignant Disease, and of Estimating Suitable Dosages, Boston M. & S. J. **177**:787 (Dec. 6) 1917.

4. Redfield, A. C., and Bright, E. M.: Hemolytic Action of Radium Emanation, Am. J. Physiol. **65**:312 (July) 1923; The Physiological Action of Ionizing Radiations, ibid. **68**:354 (April) 1924.

5. Minot, G. R., and Weld, M.: Unpublished observations.

6. Ashby, W.: A Study of the Mechanism of Change in Resistance of Erythrocytes to Hypotonic Salt Solutions, Am. J. Physiol. **68**:250 (April) 1924.

the only proper controls for the experiments described are tests on red cells from the same animals that have stood for the same amount of time as those subjected to the various procedures.

2. *Effect of Lead.*—Aub, Reznikoff and Smith [2] have shown that when erythrocytes are exposed to 0.01 mg. of lead as chlorid per cubic centimeter of cell suspension, their resistance to hypotonic salt solutions is greatly increased. The degree of this action of lead depends on the concentration, the time of exposure and the temperature. These investigators did not determine a difference in the effect of lead on immature and mature red corpuscles. In the experiments here reported it was repeatedly noted that lead affected the resistance of

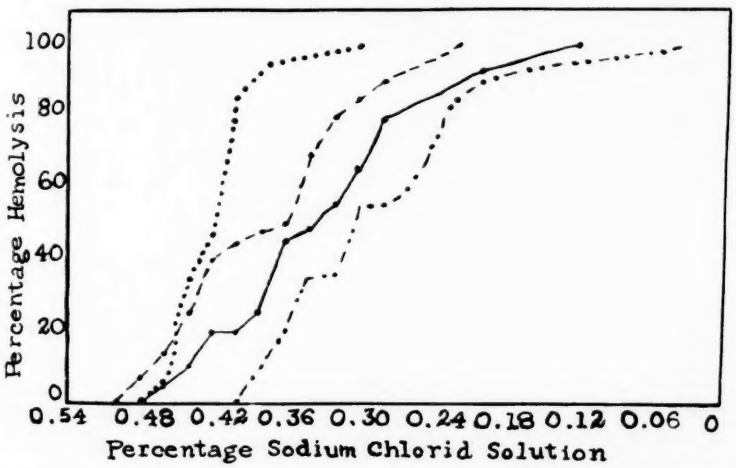

Fig. 1.—Effect of lead on "fragility" of mature and immature erythrocytes: dotted line, control adult cells; dots and dashes, treated adult cells; broken line, control immature cells; solid line, treated immature cells.

erythrocytes from a normal rabbit much more than it did those from an anemic animal having a large number of immature red cells. This finding was constantly observed and is illustrated in Figure 1. The figure shows that the difference between the point of complete hemolysis of the mature "leaded" cells and their control and between the immature "leaded" cells and their control is in the ratio 2.5 : 1. Although the differences between the points of initial hemolysis are not so great, yet the "resistance span" (the range between initial and complete hemolysis) of the adult "leaded" cells is greater than that of the young "leaded" cells. The degree of difference apparently fluctuated with the relative number of immature cells present, but the greater effect of lead on adult cells than on young cells was a constant finding.

3. *Effect of Radium.*—Irradiation from radium emanation did not affect the resistance of either immature or adult cells to hypotonic salt solutions. As is shown in Figure 2 the curves for the percentage of hemolysis of the control and irradiated cells do not vary beyond the range of experimental error.

4. *Effect of Lead and Radium.*—The experiments showed that when adult or immature cells are exposed to lead and then to radium the effect produced on their fragility to saline solutions is midway between the effect of either alone. Figures 1, 2 and 3 show that lead tends to lengthen the "resistance span," radium tends to make it similar to the control, but when both lead and radium are used the curve is a combination of these two effects.

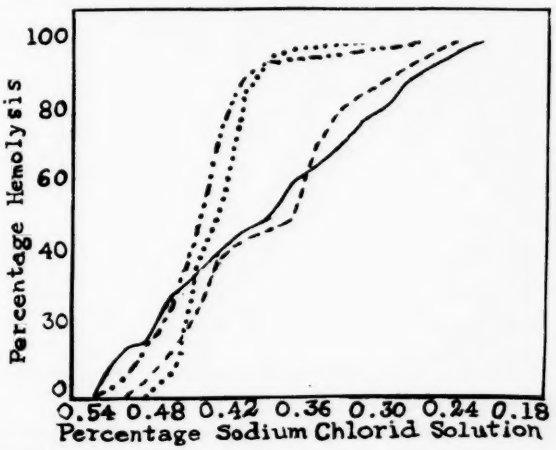

Fig. 2.—Effect of radium on "fragility" of mature and immature erythrocytes: dotted line, control adult cells; dots and dashes, treated adult cells; broken line, control immature cells; solid line, treated immature cells.

Thus, erythrocytes have an increased resistance to hemolysis by hypotonic salt solutions following chronic blood loss, on standing several hours in Ringer's solution, and after exposure to lead, while their resistance is unchanged by radium emanation. However, the foregoing experiments do not furnish information concerning the destructive action of radio-active substances on cells containing a heavy metal. For this purpose, one must turn to the direct hemolytic action of the substances employed.

THE HEMOLYTIC ACTION OF LEAD AND RADIUM

Numerous experiments were conducted to determine the hemolytic effect of lead, radium, and lead and radium combined on both immature and adult red cells.

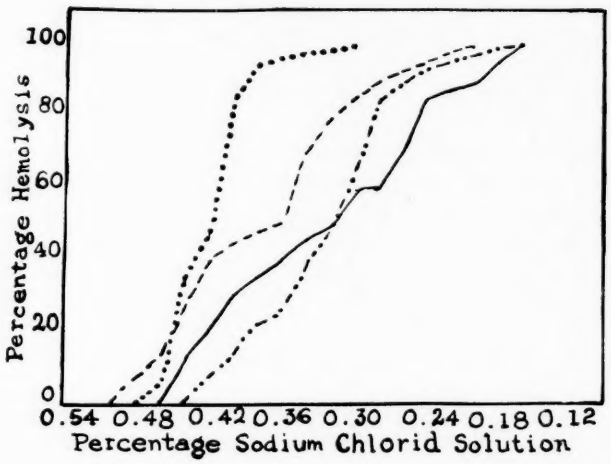

Fig. 3.—Effect of lead and radium on "fragility" of mature and immature erythrocytes: dotted line, control adult cells; dots and dashes, treated adult cells; broken line, control immature cells; solid line, treated immature cells.

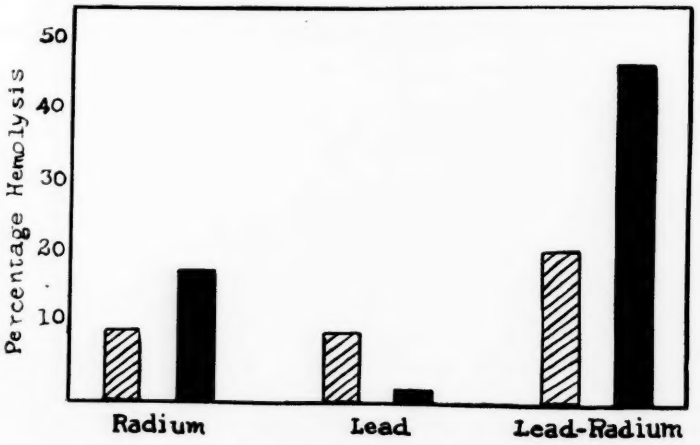

Fig. 4.—Hemolytic effect of lead, radium, and lead and radium on mature and immature erythrocytes: broken lines, adult cells; solid lines, immature cells.

Red blood corpuscles, when gently defibrinated, carefully washed, and centrifugated are not hemolyzed. Their exposure to a sufficient amount of lead causes them to become very brittle, as Aub, Reznikoff and Smith [2] have shown. In the experiments recorded below manipulation of these "leaded" cells was done with the greatest care to prevent hemolysis by trauma. Old and young cells were subjected to the action of lead, radium, and lead and radium by the methods described above.

The results obtained in five typical experiments conducted to determine the hemolytic effect of lead and radium on old and young cells are summarized and shown graphically in Figure 4. It will be observed that the adult cells are more easily hemolyzed by lead than are the immature cells, while radium affects the cells in just the opposite manner. The irradiation of cells previously exposed to lead causes a marked increase in the amount of hemolysis. This destructive action is twice as marked on young cells as on adult cells.

The Hemolytic Effect of Various Exposures of "Leaded" Immature and Mature Erythrocytes to Radium Emanation

Time of Exposure to One Millicurie of Radium Emanantion	Percentage of Hemolysis of Immature Cells*	Percentage of Hemolysis of Adult Cells†
½ hour	5	2
1 hour	53	25
1½ hours	80	35

* Erythrocytes from a rabbit having 2,100,000 per cubic millimeter; hemoglobin, 35 per cent., Sahli; reticulocytes, 46 per cent.

† Erythrocytes from a rabbit having 5,600,000 per cubic millimeter; hemoglobin, 101 per cent., Sahli; reticulocytes, 1.5 per cent.

The effect of radium was so greatly enhanced by the secondary radiation obtained from the presence of lead that determinations were made of the influence of various lengths of exposure of "leaded" cells to the radio-active substance. Because of the difficulty of accurately measuring the small amount of emanation used a constant amount of radium was employed and the time of exposure varied. The results of a typical experiment are given in the accompanying table. The data illustrate that the hemolytic action of radium rays in the presence of a heavy metal varies with the length of exposure. Even so, the effect on young red cells bears a constant relationship to that on mature erythrocytes, while the degree of hemolysis depends on the amount of irradiation.

COMMENT

The observations on the "fragility" of old and young red blood corpuscles in hypotonic sodium chlorid solutions after exposure to lead, radium and combinations of the two, are set forth without further comment. They serve to indicate distinctions between old and young red cells. These "fragility" tests when compared with those on the hemolytic effects of lead and radium also illustrate that one form of

injury to a cell does not necessarily indicate that a similar effect will occur from other deleterious agents.

Henri and Mayer,[7] Chambers and Russ,[8] Solmanson and Dreyer,[9] Hansman,[10] and Redfield and Bright [4] have shown that radium rays have the ability to hemolyze red blood corpuscles. The alpha particles are chiefly responsible for this action.[11] In the experiments here reported alpha, beta and gamma rays of the emanation have been in solution in the red cell suspensions. This permits only one one-hundredth as much emanation to produce the same results as when beta and gamma rays alone are used.[4]

It is well known that when radio-active rays are absorbed by matter secondary radiations are liberated. If the radiator be a metal the intensity of this emission increases with the atomic weight of the metal, but the penetrating power of the rays is unaltered.[12] Redfield and Bright [4] have shown that the penetration of the secondary corpuscular radiation into protoplasm is in the range of 0.003 cm. Hence, in the case of erythrocytes the effect is largely on the cell membrane. From the work of Aub, Reznikoff and Smith [2] it is evident also that lead acts on the surface of erythrocytes. These facts explain clearly why the experiments demonstrate that the hemolytic action of radium emanation on erythrocytes is greatly increased by the presence of a heavy metal. The "leaded" red blood corpuscles were bombarded by the rays of the emanation and it is very probable had generated in their cell membranes an intense amount of secondary radiation with consequent damage to the membranes and hemolysis.

The question arises why lead hemolyzes the mature more than it does the immature red cells. This may be because young erythrocytes are of a firmer composition than old ones, as is suggested by the greater resistance of immature cells to heat.[13] Furthermore, as Buckman and MacNaugher [14] have shown, normal young red cells appear to with-

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7. Henri, V., and Mayer, A.: Action des radiations du radium sur les colloides, l'hemoglobine, les ferments et les gloubules rouges, Compt. rend. Acad. d. sc. **138**:521, 1904.

8. Chambers, H., and Russ, S.: The Action of Radium Radiations Upon Some of the Main Constituents of Normal Blood, Proc. Roy. Soc. **84**:124, 1911-1912.

9. Solmanson, C. J., and Dreyer, G.: De la loi de l'effet hémolytique des rayons d Becquerel, Compt. rend. Acad. d. sc. **144**:999, 1907.

10. Hansman, W.: Ueber Hämolyse durch Radium strahlen, Wien. klin. Wchnschr. **29**:1289, 1916.

11. Chambers and Russ (Footnote 8). Redfield and Bright (Footnote 4).

12. Sadler, C. A.: Homogeneous Corpuscular Radiation, Philosophical Mag. **19**:337, 1910.

13. Isaacs, R.; Brock, B., and Minot, G. R.: The Resistance of Immature Erythrocytes to Heat, J. Clin. Invest. **1**:425 (June) 1925.

14. Buckman, T. E., and MacNaugher, E.: The Relative Fragility of Reticulated Red Corpuscles, J. M. Research **44**:61 (Sept.) 1923.

stand hemolysis by hypotonic salt solution better than do adult cells. This property of immature erythrocytes may be analogous to their greater resistance to the injurious effect of lead. Another factor of influence is perhaps the difference in the chemical composition of cells of different ages. It is believed by many that young cells of various types have a higher phosphorus content than old cells. Buckman, Minot, Daland and Weld [15] have pointed out that this appears to be true for immature red blood corpuscles. The action of lead on red cells has been explained clearly by Aub, Reznikoff and Smith [2] to be due to its union with the inorganic phosphates of the cell. These authors likewise have shown that the diffusion of the inorganic phosphates from the red blood corpuscles into the surrounding medium prevents the action of lead on the cell. It will be recalled that in the tests recorded above the erythrocytes were suspended in Ringer's solution before adding an equal volume of 0.001 per cent lead chlorid solution. It is possible that by virtue of a higher phosphate content of the immature cells more phosphates diffused into the Ringer's solution and thus prevented the effect of the lead on these cells.

The destructive action of radio-active rays is always more marked on immature than on mature cells. Thus, it was to be expected that radium emanation would cause greater hemolysis of young than of old red blood cells. The experiments also demonstrate that a given amount of lead and radium combined hemolyze about twice as many immature corpuscles as mature ones. It is plausible to believe that these result from the damage produced by the secondary radiation emanating from the insoluble lead phosphate present on the cell membrane. Even though, as suggested above, less lead may be present on young than on old cells, it may well be that, like human tumors, an increase in irradiation injures immature much more than mature cells.

It is not intended to convey the impression that the experiments here presented have a direct bearing on the therapy of malignant disease. The fact that a heavy metal increases the destructive effect of radio-active substances and that this action is more pronounced on immature than mature red cells might be applied to the treatment of cancer. However, to do so it is necessary to find a metal of sufficiently high atomic weight which concentrates in the tumor in amounts adequate to give effective therapeutic results. The report by Bell [16] concerning the treatment of 122 patients with cancer by intravenous injections of different lead compounds is interesting in this connection. This author reports favorable results, but does not appear to have presented evi-

15. Buckman, T. E.; Minot, G. M.; Daland, G. A., and Weld, M.: Blood Phosphorus: Its Relation to Cancer and Anemia, Arch. Int. Med. **34:181** (Aug.) 1924.

16. Bell, W. B.: The Influence of Lead on Normal and Abnormal Cell Growth, Lancet **1:267** (Feb. 9) 1924.

dence that lead actually enters the tumor. Some results obtained by Minot [17] tend to show that after intravenous injection of lead compounds into mice with tumors only minute amounts of lead may be found in the cancer, while the major part of that injected is present in other parts of the body.

SUMMARY

1. Control tests confirm the work of others that erythrocytes following chronic blood loss, on standing several hours in Ringer's solution, and after exposure to lead as chlorid have an increased resistance to hemolysis by hypotonic saline solutions.

2. The "fragility" to hypotonic saline solutions of young and old erythrocytes previously subjected to lead, radium emanation and combinations of the two is as follows:

(*a*) Lead produces a greater increased resistance of mature than immature red blood corpuscles.

(*b*) Irradiation with radium emanation does not change the resistance of mature or immature erythrocytes.

(*c*) Lead and radium combined produce an effect midway between the effect of either alone.

3. The hemolytic action of lead, radium emanation and lead and radium combined on young and old erythrocytes is as follows:

(*a*) Radium hemolyzes more readily immature than mature red blood corpuscles.

(*b*) Lead has just the opposite effect from radium.

(*c*) Irradiation of "leaded" erythrocytes greatly increases the amount of hemolysis above that produced by either agent alone. This effect is twice as great on "leaded" immature as on "leaded" mature red blood corpuscles.

17. Minot, A. S.: Personal communication to the author.

BLOOD CHANGES IN THE ANTEPARTUM AND THE POSTPARTUM PERIOD OF YOUNG MOTHERS *

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Some work in Harlem Hospital in which we were attempting to ascertain the factor that predisposes children to rickets by a systematic survey of the phosphorus of the blood of mothers and infants suggested a study of wider scope, including not only the inorganic phosphorus but also other constituents of the blood during the critical period of child formation in the uterus.

Early investigators have had continual controversies regarding the significant chemical changes that occur in the inorganic constituents of normal pregnant women. The recent work of Denis and King [1] in which from 9 to 11 mg. per hundred cubic centimeters of blood is accepted as representing the standard for normal serum calcium is corroborative of these earlier studies in which no change was predicated. Of all the workers in the field, however, Widdows [2] is the only one who reaches her conclusion by analyses of the blood of the same woman at definite periods of pregancy. She finds that in most, but not in all, cases there is a tendency to a decrease in the calcium content of the blood in late pregnancy and a general tendency to rise directly after confinement, and Denis and King admit that "whether it would have been possible to demonstrate a progressive lowering of the serum calcium in individual cases, had they been able to obtain specimens of blood from the same subjects at different times during pregnancy, could only be shown by further work on this subject."

We have undertaken this further work and included in our study not only the calcium factor but also phosphorus and creatinine of the blood, as well as creatinine of the urine. Furthermore, the work was extended to include the antepartum and the postpartum periods.

Our samples of blood were taken by means of a venous puncture in the afternoon, about four hours after dinner, and immediately

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* From the chemical research laboratory of Fordham University and the chemical laboratory of Harlem Hospital.

1. Denis, W., and King, E. L.: Am. J. Obst. & Gynec. **7**:253 (March) 1924; ibid. **7**:409 (April) 1924.

2. Widdows, S. T.: Biochem. J. **17**:34, 1923.

analyzed. Lithium citrate was used as the anticoagulant. The twenty-four hour specimen urines were collected in the usual way. All the phosphorus and creatinine determinations were made on whole blood; the calcium analyses, on blood serum.

The value of any work may be estimated according to the methods used. For this reason we have adopted the following procedures: The calcium was determined by the technic of Kramer and Howland.[3] Three cubic centimeters of citrated whole blood was placed in a 15 cc. centrifuge tube and centrifugated for five minutes. One cubic centimeter of the blood plasma was pipetted with an Ostwald pipet into a dry 15 cc. centrifuge tube. To this was added 1 cc. of a saturated solution of ammonium oxalate, after which the tube was rotated to mix the contents thoroughly and then set aside for one-half hour to allow precipitation. Once more the tube was centrifugated for five minutes and the supernatant fluid decanted. The precipitate was washed with 2 per cent ammonium hydroxide, centrifugated and again decanted. This procedure was repeated three times. Five cubic centimeters of 5 per cent sulphuric acid was then added, and the tube placed in a boiling water bath for five minutes. The liberated oxalic acid was then titrated with hundredth normal potassium permanganate, and the calcium determined by a factor.

The inorganic phosphorus was determined by the original method of Bell and Doisy.[4] This consists in precipitating the proteins with trichloracetic acid, centrifugating, decanting the filtrate and precipitating the phosphorus with a solution of strychnine molybdate. After these operations had been performed the tube was centrifugated and the supernatant liquid decanted. This procedure was repeated three times. Finally the washed precipitate was dissolved in 6 cc. of tenth normal sodium hydroxide, and the solution poured into a 200 cc. volumetric flask. The test tube also was rinsed with distilled water into the same flask. Twenty cubic centimeters of 20 per cent potassium ferrocyanide was then added and also 10 cc. of concentrated hydrochloric acid. The contents of the flask was then diluted to the mark with distilled water, thoroughly mixed, and matched against a standard solution whose phosphorus had gone through a similar procedure.

The Folin-Wu [5] method was employed for the estimation of creatinine of the blood. Twenty-five cubic centimeters of a saturated solution of purified picric acid was transferred to a small clean flask and 5 cc. of 10 per cent sodium hydroxide added. Ten cubic centimeters of blood filtrate was transferred into a small flask at the same time. Five

3. Kramer, B., and Howland, J.: J. Biol. Chem. **43**:35 (Aug.) 1920.
4. Bell, R. D., and Doisy, E. A.: J. Biol. Chem. **44**:55 (Oct.) 1920.
5. Folin, O., and Wu, H.: J. Bol. Chem. **38**:81 (May) 1919.

cubic centimeters of standard creatinine was diluted to 20 cc. in another flask, then 5 cc. of freshly prepared alkaline picrate solution was added to the blood filtrate, and 10 cc. to the diluted creatinine solution. After ten minutes the two solutions were compared in the colorimeter.

The original Folin [6] method was used for the estimation of creatinine in the urine. One tube of the colorimeter was almost filled with 0.5 normal potassium bichromate and set to read 8 mm. Two cubic centi-

TABLE 1.—*Calcium in Blood (Milligrams per Hundred Cubic Centimeters)*

Case	Age	Weight	Residence	Antepartum by Months				Postpartum by Weeks					
				6	7	8	9	1	2	3	4	5	6	7
1	18	121 (54.9 Kg.)	New York	12.08	11.89	11.98	10.10	11.31	.....	10.49	11.60	11.22	10.98	11.37
				11.44	11.10	11.41	12.00	10.96	.....	10.53	11.32	12.20	10.74	11.80
				11.21	12.12	11.37	11.06	11.71	.....	.....	11.41	11.91	11.00	.....
				11.93	11.86	.....	11.42	9.60	.....	.....	.....	11.33	10.99	.....
2	14	119 (54 Kg.)	New York	.....	.....	.....	10.20	.....	.....	.....	.....	.....	.....	.....
				.....	.....	.....	10.70	.....	.....	.....	.....	.....	.....	.....
				.....	.....	.....	9.10	.....	.....	.....	.....	.....	.....	.....
				.....	.....	11.60	.....	.....	.....	.....	.....	.....	.....	.....
3	15	100 (45.4 Kg.)	Long Island	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
				.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
				.....	.....	.....	9.53	.....	.....	.....	.....	.....	.....	.....
				.....	.....	.....	11.20	.....	.....	.....	.....	.....	.....	.....
4	17	135 (61.2 Kg.)	New York	.....	.....	.....	.....	11.47	10.72	.....	.....	.....	.....	.....
				.....	.....	.....	9.83	9.10	10.88	.....	.....	.....	.....	.....
				.....	.....	.....	9.99	9.30	.....	.....	.....	.....	.....	.....
				.....	.....	.....	11.29	.....	.....	.....	.....	.....	.....	.....
5	14	120 (54.4 Kg.)	Virginia	.....	.....	.....	10.35	10.32	.....	.....	.....	.....	.....	.....
				.....	.....	.....	11.29	11.55	.....	.....	.....	.....	.....	.....
				.....	.....	.....	11.43	10.93	.....	.....	.....	.....	.....	.....
				.....	.....	10.66	.....	11.06	.....	.....	.....	.....	.....	.....
6	16	152 (68.9 Kg.)	South Carolina	.....	.....	11.73	12.40	10.37	.....	.....	.....	.....	.....	.....
				.....	.....	13.49	11.87	11.36	.....	.....	.....	.....	.....	.....
				.....	11.82	11.65	11.21	11.42	.....	.....	.....	.....	.....	.....
				.....	.....	10.88	11.61	.....	.....	.....	.....	.....	.....	.....
7	18	180 (81.6 Kg.)	Virginia	.....	11.21	12.00	12.14	.....	.....	.....	.....	.....	.....	.....
				.....	10.36	11.93	12.20	.....	.....	.....	.....	.....	.....	.....
				10.53	10.48	11.06	11.90	.....	.....	.....	.....	.....	.....	.....
				10.57	11.21	11.39	12.31	.....	.....	.....	.....	.....	.....	.....
8	19	120 (54.4 Kg.)	New York	.....	.....	.....	10.76	11.98	.....	.....	.....	.....	.....	.....
				.....	.....	.....	11.64	10.42	.....	.....	.....	.....	.....	.....
				.....	.....	.....	11.55	11.33	.....	.....	.....	.....	.....	.....
9	18	170 (77.1 Kg.)	North Carolina	.....	.....	.....	.....	.....	10.89	.....	.....	.....	.....	.....
				.....	.....	.....	10.34	11.91	10.57	.....	.....	.....	.....	.....
				.....	.....	.....	.....	.....	11.36	.....	.....	.....	.....	.....
				.....	.....	.....	11.56	11.46	.....	.....	.....	.....	.....	.....
10	13	128 (57.1 Kg.)	South Carolina	.....	.....	.....	.....	12.27	.....	.....	.....	.....	.....	.....
				.....	.....	.....	.....	12.39	.....	.....	.....	.....	.....	.....
				.....	.....	.....	.....	11.77	.....	.....	.....	.....	.....	.....
				.....	.....	.....	12.11	.....	.....	.....	.....	.....	.....	.....

meters of urine was pipetted into a 100 cc. volumetric flask, to which was then added 3 cc. of saturated picric acid solution and 1 cc. of 10 per cent sodium hydroxide. After five minutes the contents of the flask were diluted to the mark, thoroughly mixed and compared with the standard.

In our study we have confined ourselves to young negro girls, some of whom were born and bred in the South while others had been in

6. Folin, O.: Ztschr. physiol. Chem. **41**:223, 1904.

New York their entire lives. These girls were kept in a home in which they were all subjected to the same dietetic and hygienic conditions, eating the same food, and spending a similar number of hours in the open air. All of them showed negative Wassermann reactions and were primiparas. The blood and urine analyses, with only a few exceptions, were made every week. Unfortunately, our earliest admittance dates from the sixth month of gestation.

TABLE 2.—*Inorganic Phosphorus in Blood (Milligrams per Hundred Cubic Centimeters)*

Case	Age	Weight	Residence	Antepartum by Months				Postpartum by Weeks						
				6	7	8	9	1	2	3	4	5	6	7
1	18	121 (54.9 Kg.)	New York	2.41	2.19	2.54	2.22	1.98	....	2.03	1.76	1.65	2.32	2.31
				2.39	2.30	2.01	2.31	2.31	2.17	2.11	1.89	1.88	2.14	2.47
				2.09	2.00	2.16	2.18	2.16	....	....	2.40	2.10	2.20	....
				2.13	2.09	....	2.05	2.33	....	....	2.36	1.92	2.23	....
2	14	119 (54 Kg.)	New York	....	....	....	2.92	....	....	....	....	....	....	....
				....	....	....	2.76	....	....	....	....	....	....	....
				....	....	....	2.59	....	....	....	....	....	....	....
				....	....	2.60	....	....	....	....	....	....	....	....
3	15	100 (45.4 Kg.)	Long Island	....	....	....	....	....	....	....	....	....	....	....
				....	....	....	....	....	....	....	....	....	....	....
				....	....	....	2.70	....	....	....	....	....	....	....
				....	....	....	2.60	....	....	....	....	....	....	....
4	17	135 (61.2 Kg.)	New York	....	....	....	....	3.61	3.21	....	....	....	....	....
				....	....	....	3.00	2.99	2.87	....	....	....	....	....
				....	....	....	3.12	2.74	....	....	....	....	....	....
				....	....	....	3.10	....	....	....	....	....	....	....
5	18	120 (54.4 Kg.)	Virginia	....	....	....	2.60	3.22	....	....	....	....	....	....
				....	....	....	2.33	3.00	....	....	....	....	....	....
				....	....	....	2.65	3.10	....	....	....	....	....	....
				....	....	2.40	....	2.76	....	....	....	....	....	....
6	16	152 (68.9 Kg.)	South Carolina	....	....	2.56	2.77	2.96	....	....	....	....	....	....
				....	....	2.70	2.32	2.54	....	....	....	....	....	....
				....	....	2.98	2.47	2.41	....	....	....	....	....	....
				....	2.54	2.74	2.61	....	....	....	....	....	....	....
7	18	180 (81.6 Kg.)	Virginia	....	2.90	2.64	2.53	....	....	....	....	....	....	....
				....	1.86	2.33	2.70	....	....	....	....	....	....	....
				3.10	2.47	2.70	2.44	....	....	....	....	....	....	....
				2.51	2.82	2.71	....	....	....	....	....	....	....	....
8	19	120 (54.4 Kg.)	New York	....	....	....	3.25	2.50	....	....	....	....	....	....
				....	....	....	2.92	2.99	....	....	....	....	....	....
				....	....	....	2.37	2.76	....	....	....	....	....	....
9	18	170 (77.1 Kg.)	North Carolina	....	....	....	....	....	2.82	....	....	....	....	....
				....	....	....	2.95	2.85	2.51	....	....	....	....	....
				....	....	....	....	....	2.77	....	....	....	....	....
				....	....	....	2.44	2.44	....	....	....	....	....	....
10	13	128 (57.1 Kg.)	South Carolina	....	....	....	....	2.10	....	....	....	....	....	....
				....	....	....	....	2.06	....	....	....	....	....	....
				....	....	....	....	2.35	....	....	....	....	....	....
				....	....	....	2.30	....	....	....	....	....	....	....

The calcium determinations are given in table 1. In our studies these analyses were not made in random cases, as was true of the work of Denis and King, but on women throughout their entire gestation period, and in this respect the study resembles that of Widdows. The findings, however, are more in harmony with the work of Denis inasmuch as there was no significant change up to parturition. In these young women the calcium concentration was found to be 11.3 mg. per hundred cubic centimeters, which is a trifle more than the 10.9 mg.

found by Denis in her cases. It is to be noted, however, that the patients presented by Denis were mostly mature women and with a varying number of pregnancies. In only one of our cases was there an increase in the calcium content from the sixth to the ninth month ranging from 10.5 to 12.1 mg. per hundred cubic centimeters, which in this instance was diametrically opposed to the findings of Widdows. With parturition there was a slight drop in the calcium, which lasted for three weeks and then returned to normal for this particular group. This

TABLE 3.—*Creatinine in Blood (Milligrams per Hundred Cubic Centimeters)*

Case	Age	Weight	Residence	Antepartum by Months				Postpartum by Weeks					
				6	7	8	9	1	2	3	4	5	6
1	18	121 (54.9 Kg.)	New York	1.72	1.96	2.14	2.20	1.85	....	1.52	2.22	2.10	2.27
				1.79	2.12	2.33	2.16	2.13	....	1.37	2.01	2.17	2.31
				2.23	2.18	1.98	2.41	2.00	....	1.40	1.88	2.14	....
				2.15	2.30	....	2.18	1.61	....	....	1.98	1.92	....
2	14	119 (54 Kg.)	New York	....	....	....	....	....	....	....	....	....	....
				....	....	....	2.40	....	....	....	....	....	....
				....	....	....	2.63	....	....	....	....	....	....
				....	....	2.37	2.15	....	....	....	....	....	....
3	15	100 (45.4 Kg.)	Long Island	....	....	....	....	....	....	....	....	....	....
				....	....	....	....	....	....	....	....	....	....
				....	....	....	1.62	....	....	....	....	....	....
				....	....	....	1.40	....	....	....	....	....	....
4	17	135 (61.2 Kg.)	New York	....	....	....	....	2.33	2.13	....	....	....	....
				....	....	....	2.19	2.18	1.79	....	....	....	....
				....	....	....	2.50	2.44	....	....	....	....	....
				....	....	....	2.46	....	....	....	....	....	....
5	18	120 (54.4 Kg.)	Virginia	....	....	....	1.54	1.22	....	....	....	....	....
				....	....	....	1.80	1.56	....	....	....	....	....
				....	....	....	1.60	2.01	....	....	....	....	....
				....	....	1.83	....	1.75	....	....	....	....	....
6	16	152 (68.9 Kg.)	South Carolina	....	....	2.03	2.22	1.98	....	....	....	....	....
				....	....	2.56	2.20	2.12	....	....	....	....	....
				....	....	2.41	1.87	2.16	....	....	....	....	....
				....	1.66	2.13	2.04	....	....	....	....	....	....
7	18	180 (81.6 Kg.)	Virginia	....	1.63	1.75	2.30	....	....	....	....	....	....
				....	1.72	2.09	2.17	....	....	....	....	....	....
				2.14	1.98	2.06	1.88	....	....	....	....	....	....
				2.18	1.50	1.76	2.15	....	....	....	....	....	....
8	19	120 (54.4 Kg.)	New York	....	....	....	2.10	2.40	....	....	....	....	....
				....	....	....	2.15	2.60	....	....	....	....	....
				....	....	....	2.27	2.33	....	....	....	....	....
9	18	170 (77.1 Kg.)	North Carolina	....	....	....	....	....	1.84	....	....	....	....
				....	....	....	2.12	2.20	2.00	....	....	....	....
				....	....	....	....	....	2.01	....	....	....	....
				....	....	....	1.73	2.33	....	....	....	....	....
10	13	128 (57.1 Kg.)	South Carolina	....	....	....	....	2.63	....	....	....	....	....
				....	....	....	....	2.19	....	....	....	....	....
				....	....	....	....	2.33	....	....	....	....	....
				....	....	....	2.17	....	....	....	....	....	....

is obviously interrelated with the carbon dioxide capacity of the blood, since carbon dioxide determinations made during the postpartum period showed that immediately after delivery the carbon dioxide combining power of the blood dropped to about 30 with a gradual rise to normality up to the time of dismissal.

A detailed study of the table of the calcium in the blood brings out the interesting fact that the northern girls have a lower calcium concentration than the southern girls, the figures being 10.6 and 11.5 mg.,

respectively. The cases reported by Denis which are in all respects comparable with those reported here, with the exception of gestation months, come to an average of 10.8 mg., which is identical with the average of our northern girls.

Hess,[7] and later Denis, have reported inorganic phosphorus as being normal during pregnancy. This is confirmed by our data (table 2). In the postpartum period, however, we have found a slight drop, which

TABLE 4.—*Creatinine in Urine (Milligrams per Twenty-Four Hour Output)*

Case	Age	Weight	Residence	Antepartum by Months				Postpartum by Weeks					
				6	7	8	9	1	2	3	4	5	6
1	18	121 (54.9 Kg.)	New York	677	570	712	412	182	...	250	492	310	...
				493	826	...	592	275	...	264	...	200	307
				702	...	736	644	429	640	483	...	438	...
				...	641	...	487	...	...	...	...	...	...
2	14	119 (54 Kg.)	New York	...	...	...	...	...	...	...	...	...	...
				...	...	609	579	...	...	...	...	...	...
				...	...	533	422	...	...	...	...	...	...
				...	...	601	...	...	...	...	...	...	...
3	15	100 (45.4 Kg.)	Long Island	...	...	...	398	...	...	...	...	...	...
				...	...	...	...	...	...	...	...	...	...
				...	...	...	650	...	...	...	...	...	...
				...	...	...	711	...	...	...	...	...	...
4	17	135 (61.2 Kg.)	New York	...	...	...	...	200	124	...	...	...	...
				...	...	...	572	292	186	...	...	...	...
				...	...	...	759	313	...	...	...	...	...
				...	...	...	793	...	...	...	...	...	...
5	14	120 (54.4 Kg.)	Virginia	...	...	...	...	174	...	...	...	...	...
				...	...	...	491	332	...	...	...	...	...
				...	...	...	587	301	...	...	...	...	...
				...	...	636	...	...	...	...	...	...	...
6	16	152 (68.9 Kg.)	South Carolina	...	...	...	497	150	...	...	...	...	...
				...	476	442	...	231	...	...	...	...	...
				...	632	581	...	262	...	...	...	...	...
				...	595	730	429	...	...	...	...	...	...
7	18	180 (81.6 Kg.)	Virginia	637	685	462	...	...	...	...	...	...	...
				561	574	...	495	...	...	...	...	...	...
				772	713	600	629	...	...	...	...	...	...
				...	...	558	...	...	...	...	...	...	...
8	19	120 (54.4 Kg.)	New York	...	...	...	590	140	...	...	...	...	...
				...	...	...	676	390	...	...	...	...	...
				...	...	...	459	271	...	...	...	...	...
9	18	170 (77.1 Kg.)	North Carolina	...	...	...	...	...	220	...	...	...	...
				...	...	...	613	306	146	...	...	...	...
				...	...	...	723	359	...	...	...	...	...
				...	...	...	519	...	...	...	...	...	...
10	13	128 (57.1 Kg.)	South Carolina	...	...	...	...	141	...	...	...	...	...
				...	...	...	814	198	...	...	...	...	...
				...	...	...	733	285	...	...	...	...	...
				...	...	...	628	...	...	...	...	...	...

may be significant, occurring in the third, fourth and fifth week after parturition. This slight drop, if it is significant, may be associated with the regeneration of impaired tissue. In the individual cases there was no significant difference between the average of the northern girl and that of the southern girl.

The creatinine content of the blood (table 3) of pregnant women has been determined in scattered cases by Denis and her co-workers and

7. Hess, A. F., and Matzner, M. J.: Am. J. Dis. Child. **26**:285 (Sept.) 1923.

also by Killian and one of us.[8] Both of these found creatinine within normal limits, the former worker giving figures of a low norm whereas the latter gives figures within the high range of normal concentration. In our data most of the analyses were within the high range and the averages of the various months of gestation show no significant change. The postpartum period also shows no changes.

Creatinine was also determined in the urine. The analyses are given in table 4, and are tabulated in milligrams for the twenty-four hour output. During the development of the fetus the creatinine of the blood was found to maintain a constant normal level for which the normal function of the kidney is responsible. When, however, the creatinine of the urine is examined, it is found that during pregnancy the amount eliminated in the course of the day is considerably more than that recorded for normal women. This high creatinine value drops immediately after delivery to quantities that are almost identical with those reported for normal women. The average for the pregnant months is 630 mg. per twenty-four hours, and for the weeks following parturition, 340 mg.

TABLE 5.—*Summary of Complete Data*

	Antepartum by Months				Postpartum by Weeks						
	6	7	8	9	1	2	3	4	5	6	7
Inorganic phosphorus in blood	2.44	2.35	2.57	2.61	2.64	2.32	2.07	2.10	1.89	2.22	2.39
Calcium concentration in blood	11.29	11.33	11.62	11.14	11.09	10.87	10.51	11.44	11.66	11.18	11.58
Creatinine in blood	2.03	1.89	2.09	2.07	2.11	1.98	1.43	2.02	2.08	2.29	....
Creatinine in urine	640	634	642	593	256	263	332	492	316	307	...

CONCLUSION

It is hardly necessary to emphasize the fact that many difficulties surround the study of mineral metabolism, and that as a result we have relatively no trustworthy information about the subject. It is certain that the minerals are essential to normal growth and nutrition, and one can easily appreciate the far greater importance these factors assume when the discussion concerns pregnancy.

The formation of the fetus involves not only ordinary growth but also an enormous growth of bone tissue. Calcium, together with phosphorus, is important in bone formation. Calcium also plays a significant rôle in the coagulation of the blood, the contraction of muscle, the permeability of cells and the regulation of blood sugar. The softening of the teeth and the concomitant tendency to decay during pregnancy may be due to the lack of sufficient calcium in the diet to supply both the fetus and the mother.

8. Sherwin, C. P., and Killian, J. A.: Am. J. Obst. & Gynec. **2**:6 (July) 1921.

The phosphorus is a constituent of all nuclear material, and with magnesium and calcium gives hardness to bone. Both of these materials, therefore, are intimately connected during gestation, and the fact that, despite the enormous drain on them, the mother is able to keep a normal level is both interesting and suggestive of more detailed studies.

The creatinine is a substance about which there has been considerable interest. Especially is this true of the creatinine of women. It is an index of endogenous protein metabolism, the amount of excretion varying per day and depending on the size of the individual, or rather of the protoplasmic mass. It is materially altered in physiologic crises, such as regeneration of tissues, fevers, wasting diseases, and the so-called premortal rise on prolonged fasting. For which reasons it has been considered of unusual significance during the period of the fetal growth.

In concluding, we might summarize as follows:

1. The calcium concentration of pregnant women during gestation was found to be normal, with a slight decrease immediately after parturition and a rise to high normal just before dismissal.

2. Pregnancy did not alter the phosphorus content of the blood of the group studied, nor was there any change during the postpartum period.

3. High normal concentrations of creatinine were found in the blood during the antepartum and the postpartum periods.

4. The output of creatinine in the urine was increased during the fetal formation but returned to normality immediately on parturition.